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DR. W. G. MACCALLUM, *President.*

A CASE OF ADENO-CARCINOMA OF THE CORPUS UTERI WITH PRONOUNCED METAPLASIA.

ROBERT T. FRANK, M.D.

The history showed that the patient had entered the menopause four years previously. Recently she again began to bleed, but irregularly. Curettings obtained demonstrated the presence of a carcinomatous growth. On opening the uterus a somewhat pedunculated growth, the size of a pigeon's egg, was found at the fundus, midway between the tubal openings. Macroscopically the tumor appeared like the usual type of adeno-carcinoma located in this region. Microscopically, however, direct transitions from adeno-carcinomatous formations into squamous-celled complexes could be demonstrated. No reference to such a condition was found in the literature.

There are a few reports of the coincident appearance of adeno- and squamous-celled carcinoma of the body of the uterus. However, in most of these cases there was likewise a carcinoma of the cervix, and it appears very doubtful that the squamous-celled carcinoma of the body was primary. It is more likely that in these instances the corpus growth was metastatic or a direct extension of the cervical cancer. Kaufman reported a tumor of the uterine body in which adeno- and squamous-celled carcinoma occurred together, the cervix being unaffected.

The tumor shown to-night is primarily an adeno-carcinoma. The gland complexes invade the uterine muscle. Toward the surface a gradual and unbroken transition into squamous cells becomes evident. Some "pearl" formation is seen. The squamous cells evince no tendency to invade adjacent structures. This lack of invasive qualities combined with the localization to the less well-nourished surface portions have led me to interpret the findings as a metaplasia due to nutritional causes. No epidermization of the endometrium, sometimes noted after the menopause, was encountered in other parts of the uterus.

The second case has a two-fold interest: first, because of its rarity; second, because the condition was found at such an early stage. The case is one of

PSEUDO-MYXOMA PERITONEI, ARISING FROM THE VERMIFORM APPENDIX.

This was an accidental finding during a laparotomy performed to ventrofix the uterus and remove the appendix (which had caused vague symptoms referable to the right iliac region).

The cecum was found in its normal position. It was bound down by velamentous adhesions. After these were separated, the appendix came into view behind the intestine. The appendix was found lying over the Psoas muscle, but raised away from the muscle by a thick circumscribed layer of gelatinous tissue which is best described in the words of Neumann, who reported a similar case, as a conglomeration resembling frog's spawn. The appendix and the surrounding jelly-like mass were removed in toto. Both ovaries and tubes appeared entirely normal.

The appendix macro- and microscopically proved normal. The jelly-like mass, on section, showed mucinous material, fibrin and goblet cells, such as are seen throughout the mucosa of the gastro-intestinal canal.

The cases found in the literature number only seven or eight. In all either a hernia of the mucosa or a rupture of the appendix was noted. Several recurrences are on record, in spite of the fact that all of the diseased tissue was apparently removed. Some remained permanently well after re-operation; others died of intestinal obstruction, infection, etc.

In the present case, though the outlook is slightly doubtful, the early time of operation warrants a somewhat more hopeful prognosis.

Discussion.

Dr. Mandlebaum said he recently had a case of carcinoma of the cervix uteri in which two distinct types of tumor were present, squamous as well as cylindrical. At that time, in searching through his material and getting together one hundred cases of carcinoma of the uterus, extending over a period of ten or twelve years, he found three cases of primary carcinoma of the corpus uteri, in which there was a distinct condition of metaplasia into the squamous-cell type. Although he had looked up the matter at that time, he could not find any good references in the literature as to the frequency of this condition, but in the three cases mentioned this type of metaplasia was undoubtedly present.

Dr. Frank asked Dr. Mandlebaum whether in his cases any of the squamous cells were found to invade the deeper layers of the uterus.

In answer to Dr. Frank's question, Dr. Mandlebaum stated that, as far as he could recall, the change was simply on the surface. There did not seem to be any growth into the musculature of the uterus in these cases. He also stated that in one of his three cases there were distinct epithelial pearls present.

AN EXPERIMENTAL STUDY OF THE CAUSES WHICH PRODUCE THE GROWTH OF THE MAMMARY GLAND.

ROBERT T. FRANK, M.D., AND A. UNGER, M.D.

In all mammals hyperplasia of the breast takes place during pregnancy. Shortly after the birth of the young, milk secretion sets in. Ribbert transplanted the breast of a guinea pig to the root of its ear; milk secretion occurring in a subsequent puerperium proved that breast function does not depend upon the nervous system. Basch and others have demonstrated that the quantity and composition of the milk secreted is likewise independent of nervous stimuli.

The development of the breast at puberty is dependent upon ovarian function. This is proved by the non-development consequent to early castration. The pregnancy hyperplasia has been explained in several ways.

Halban claims that the placenta stimulates breast growth. He believes that when the placenta is expelled the breast begins to secrete. His hypothesis is based upon clinical observations. In abortion when the fetus dies, if the placenta becomes functionless, milk is secreted. If the placenta is retained and functionates, milk is not produced. In hydatid mole without fetus the breast hypertrophies, etc. The placenta is the antagonist of the ovary during pregnancy and inhibits its activity.

Starling's (1906) theory of breast hyperplasia is at present the most commonly accepted. Claypon and Starling injected virgin female rabbits daily with extract of rabbit fetuses. In six out of ten experiments a varying degree of breast growth was noted. The injections were made intraperitoneally, in order not to bathe the breast tissue with proteid solution. Extracts filtered through a Berkefeld candle and boiled extracts produced these effects. Extracts of the ovary, placenta and mucous membrane of the uterus were ineffective.

Starling concluded, from these experiments, that the breast hyperplasia of pregnancy was due to a highly diffusible chemical substance present in very small quantities throughout the body of the fetus and constantly taken up by the mother's blood. This *breast hormone*, like secretin, withstands boiling. It has a specific action upon the dormant breast acini and causes them to hypertrophy. At birth the hormone's anabolic influence is removed and the hyperplastic cells begin to secrete.

Foa (1908) injected rabbits with extracts of cow's fetuses. He found that unboiled extracts of heterologous fetuses produced the same growth as that reported by Starling, but boiled extracts were ineffective.

Biedel and Koenigstein (1910) repeated and extended Starling's work, also employing rabbits. They obtained hyperplasia with homologous extracts, and with entire fetuses implanted in the peritoneal cavity. In two experiments these investigators castrated the rabbits before beginning the injections without, however, affecting the positive results.

Finally, Basch (1910) published a new theory based upon experiments on rabbits, guinea pigs, dogs and children. According to his views, the combined secretion of ovary and placenta produce the hyperplasia of the breasts. Basch gives a few details and indicates merely by inference that the injections of the placental extract were made subcutaneously. Moreover, he used chiefly multiparous animals shortly after their milk secretion had ceased. His work merits no discussion.

Our own work was nearly completed before the reports of

Basch, and Biedel and Koenigstein were published. Foa's work was not known to us at the time we began our experiments.

The object of our research was primarily to ascertain whether heterologous fetal extracts produced breast hyperplasia, in order that we might use fetuses of a readily obtainable species. It would then be possible to use large quantities of extracts and perhaps by exaggeration of stimuli transform physiological into pathological growth. Furthermore, we determined to use rats, in order to be able to study the effect of tumors transplanted into an environment subjected to artificial and controllable stimulation.

Employing Starling's technic, we injected eight white rats with extracts of cows' fetuses. No increased development of the breasts occurred.

We then repeated the experiments, using rats' fetuses, ovaries and placentæ. The results were likewise negative.

Thereupon it became necessary to control Starling's results. Using his technic, we injected three series of rabbits with extracts of rabbits' fetuses, ovaries, placentæ and hypophyses. In all, 12 animals were used. Of these 5 received extract of fetuses, 2 respectively extracts of placentæ, extracts of ovaries, and extracts of hypophyses of pregnant animals, and 1 a combined extract of ovaries and hypophyses. In the last series rabbits previously castrated were used. Not only did the results vary greatly in each series, but also showed no correspondence to the tissues used for injection. For instance, one placental animal showed more hyperplasia than any of the fetus rabbits. Two ovarian animals showed marked growth, the other hardly any, etc. We were, therefore, forced to conclude that some as yet unknown factor must be accounted for.

To discover the cause of variation we, at intervals, removed breasts from normal untreated rabbits. It soon became apparent that at different periods a marked increase in size and of functional activity may occur in the breast of virgin rabbits. At any given period all the breasts are of the same size, but when removed at successive intervals many animals show a progressive increase in size and in the number of ducts and acini.

As yet we have been unable to determine whether this change consists of a cyclical increase and decrease, such as was reported by Bouin and Ancel. In fact we have never noted a diminution in the size and extent of ducts, although regression of the acinous portions does seem to occur. The effect of castration, likewise, is not yet clearly proved. We have, however, found that no rapid involution follows removal of the ovaries.

Our specimens show that physiological hypertrophy accounts for the results obtained by Starling, Foa and Biedel and Koenigstein. The extreme differences obtained in our three series also demonstrate that the injections do not influence these physiological variations, otherwise some concordance would be noticeable. Consequently, we feel justified in concluding that Starling's theory of a fetal hormone has no basis of experimental proof.

The results of our work so far are purely destructive. We hope, however, in the near future to offer an explanation which is more in accord with the other phenomena of gestation. In the uterus certain well-understood changes take place at regular intervals, in order to prepare for a possible pregnancy. These changes are dependent upon the corpus lutem. There is some evidence that similar changes occur in the breast, and probably these, likewise, are effected by the yellow body. What factor, after impregnation, causes the persistence and exaggerated activity of the corpus lutem is quite unknown. Perhaps it is the fetus; but, if so, its action is indirect, and the necessarily crude method of injecting extract of fetuses offers little promise of solving the problem.

Dr. Frank then demonstrated lantern slides of the various forms of breasts which are found in rabbits and the changes obtained after injection of various extracts.

Discussion.

Dr. MacCallum said it seemed that the effect which Dr. Frank had shown in the menstrual changes, as bringing about difference in the size of the breasts, is extremely important and made it seem at once that this might be the explanation of the results which Starling had ascribed to his injections. He thought that Dr. Frank would surely agree, however, that there must be something in the way of a chemical substance possibly existing during the course of the menstrual changes, which acts very much more intensely during the course of pregnancy; but that this substance was not demonstrated by the injection experiments of Starling.

Under all circumstances the injection of a substance day by day seemed a very poor substitute for the gradual secretion of the living organs, and it was only in connection with the thyroid that any real approach to the functions of the organs of internal secretion had been attained by the injection of extracts.

A SARCOMA TRANSMITTED BY AN AGENT SEPARABLE FROM THE TUMOR CELLS.

PEYTON ROUS, M.D.

The decade of work with transmissible neoplasms has much increased our knowledge of tumor behavior, and has disclosed the existence of immunity processes directed against such growths; but it has scarcely affected the problem of tumor etiology. All investigations with the neoplasms of the rat, mouse and dog have failed to bring to light their cause, and they can still be transmitted only by transplanting the living cells. The present instance is the first in which it has proved possible to separate from tumor cells an agent that will cause the disease in new hosts. Since the importance of the observation depends entirely on the characters of the growth employed, these will be discussed in detail.

Description of the Tumor.

(Lantern slides and charts were shown in illustration.)

The original growth occurred in the subcutaneous tissue of an otherwise healthy chicken. The attempt to transplant it proved successful and the tumor has thus far been propagated in eleven consecutive series of fowls. Histologically it consists of spindle cells, arranged in bundles, and supported by a slight vascular framework. By means of special stains intercellular connective tissue fibrils can be demonstrated; and mucinous ground substance is sometimes found. As a rule the cells have a well-defined spindle shape, but at the edge of the growing mass they may be ovoid or polyhedral, and only later take up the spindle form. The cell nucleus is vesicular, and relatively large. Division is mostly by amitosis, though mitoses are frequent. Although the growth has been transplanted often, the morphological changes in it have been relatively slight. Microscopically it is always a spindle-celled sarcoma or myxosarcoma.

In the gross the tumor is usually firm and gristly, but it may be friable, or even gelatinous, containing in the last instance much true mucin. The color of the neoplastic tissue is grayish or yellowish white, and the cut surface finely striated. Enlargement of the mass takes place both by expansion and by active invasion and destruction of the surrounding tissues. At its center coagulation necrosis, cyst formation or hemorrhage are commonly seen. The health of the host is at first unaffected, but, with the continued growth of the neoplasm, emaciation sets in, and the fowl becomes cold, weak and, for a day or two before death, comatose.

The growth which results from an implantation of the neoplastic tissue may remain local, but more frequently metastasis takes place from it. At autopsy the lungs may be almost replaced by discrete gristly nodules which are found also in the liver, heart, and to a less extent in the other viscera. The blood-stream is the usual path of dissemination, though it may follow the lymphatics. Contact metastasis, and a scattering of the growth in the serous cavities are both frequent.

It has been of importance to determine how metastasis takes place. The histological evidence for an origin of the secondary nodules through lodgement and growth of cells detached from the primary mass is more conclusive than with most tumors. Many instances are met with in which a strand of the neoplastic tissue has penetrated one of the thin-walled blood vessels and proliferated within its lumen. Such a strand, bare of endothelium, may extend for a considerable distance in the blood stream. A study of early metastases indicates that they arise by growth from a small vessel occluded with tumor tissue. The distribution of the metastases is also such as would indicate cell-transportation, namely, to the lungs first, later to the viscera supplied by the systemic circulation. And the transplantability of the cells has been proved by a microscopic examination of grafts of the tumor tissue removed shortly after implantation.

The fate of tumor grafts in the susceptible and immune host is as follows: The bit of neoplastic tissue is vascularized within three to five days after its introduction into a susceptible fowl, and its constituent neoplastic cells survive, and proliferate, giving rise, it would seem, to all of the resulting mass. There has taken place a real transplantation of tissue. In a resistant host, on the other hand, either vascularization does not ensue, and the graft dies from lack of nourishment; or, following vascularization and transient growth, the tumor elements succumb in the midst of an accumulation of small, round cells histologically identical with lymphocytes. The second process is the one observed during the spontaneous retrogression of large growths, which occurs not uncommonly. The dwindling mass of living tumor cells is surrounded by a zone of fibrous connective tissue and is invaded here and there by lymphocytes. All these phenomena are similar to those described for the neoplasms of mammals.

Dr. James B. Murphy and I have recently transplanted the growth into developing hens' eggs, by means of a little window in the shell, which is afterwards sealed. In the embryo, or its membranes, the neoplastic cells proliferate rapidly and form within the course of a week relatively large discrete nodules. Under the microscope these consist of the characteristic spindle cells, growing in a diffuse mass, unsurrounded by cellular reaction in the host tissues. Indeed, in the susceptible adult host there is a striking absence of cellular reaction about the growing tumor.

Behavior of the Growth on Transplantation.

The original growth occurred in a pure-bred Plymouth Rock hen, and its transplantation was accomplished by the use of other individuals of the same stock. Bits of the growth were implanted in the breast muscle by means of a trochar—a procedure now the routine. For a long time the tumor could only be propagated in fowls of the variety in which it first occurred, and even yet they are much the best hosts. Repeated inoculations have been made in birds of other species and in mammals, but always with negative results. Although susceptible normal chickens and others with the tumor have been kept together in close quarters for long periods, no instance suggesting a natural infectivity of the disease has occurred.

Repeated transplantation has produced other changes in the neoplasm besides that of overcoming the specificity which at first limited its further transmission. The rate of its growth has much increased; it develops in a larger percentage of fowls of the susceptible variety; and it has acquired the power to metastasize. The growth rate is now extraordinarily rapid. A great bulging mass reaching from clavicle to groin, completely replacing the muscle and much of the subcutaneous tissue, may form in the course of three weeks after the implantation of a graft two millimeters in diameter. A majority of the living cells in such a growth will be found in process of division. Metastasis at first did not occur. Then it appeared late, infrequently, and was limited to a few organs. But now it is rarely absent in fowls dying of the disease, takes place early, and may involve many of the viscera.

Young individuals show themselves more susceptible as hosts for the transplanted growth than do old ones—a fact well known of the sarcomata of rats and mice. Until the tumor has reached a diameter of three to four centimeters, it is singularly dependent for its success on the good physical condition of the host. An intercurrent emaciating illness may entirely check its growth or even cause it to disappear, though should the fowl later recover health the tumor may return and grow rapidly. Some of the tumors of mammals exhibit a similar striking dependence on the condition of the host.

Several types of resistance to the chicken tumor have been observed, and they are similar to those already known for the transmissible neoplasms of other creatures. Reference has already been made to a resistance based on the fowl's race, and one dependent on its age. A natural resistance is met with in some young fowls of the susceptible stock. The individuals manifesting it can be inoculated again and again without success. Finally there should be mentioned an acquired resistance possessed by healthy fowls in which a tumor has retrogressed, protecting them against growth from subsequent inoculations.

The Nature of the Tumor.

Histologically the growth is a sarcoma and all the features of its behavior identify it as a malignant neoplasm—of which, indeed, it may be taken as a type instance. Our present conception of the typical malignant neoplasm is a composite derived from clinical observation, morphological findings, and the results of transmission experiments with the tumors of animals. No growth which runs its course in a single individual can yield all the features of the composite. For, although such a growth may be histologically characteristic, and perhaps metastasizes and produces a cachexia in the host, yet there exist no data as to whether, on transplantation, it would have exhibited the further features of a neoplasm. While the transmissible tumors are easily tested on these points, they, on the other hand, often lack in more obvious features, failing to infiltrate or to metastasize. It thus happens that of the many destructive neoplasms met with, comparatively few, and these of necessity transplantable, can correspond at all points with the type picture. Among them may be mentioned the Lewin carcinoma, the Flexner-Jobling carcinoma, and the sarcoma of the chicken here described.

SEPARATION OF AN AGENT CAUSING THE GROWTH.

Much of this part of the work has been done in association with Dr. James B. Murphy.

From a consideration of the histological features of the sarcoma the impression was obtained that its growth is strictly dependent on the proliferation of cells already neoplastic. There was no reason to suppose that its transmission could be accomplished in another way than by a transplantation of the cells. On this account no attempt was made to separate out an etiological agent from the growth until the increase in its malignancy had brought what seemed to be an exceptionably favorable opportunity. It was first found that the sarcoma could be produced in new hosts by the injection of fluid obtained on passing through ordinary filter paper a suspension of the ground tumor in salt solution. The fluid supernatant after long centrifugalization of a suspension also caused tumors. Resort was then had to Berkefeld filters tested under the conditions of the experiment and found to hold back *Bacillus prodigiosus.* Using a three or four per cent. suspension of the tumor in warm Ringer's solution several different filtrations were made. Relatively small amounts of the resulting fluid (0.2 to 0.5 cc.) yielded tumors in some of the susceptible hosts inoculated; in one instance where larger amounts were used (0.5 to 1.0 cc.) eighty per cent. of the fowls developed growths. The sarcomatous tissue when dried over sulphuric acid *in vacuo* retains its ability to cause the growth in new hosts. The characteristic tumor has been obtained by an inoculation of material dried to a powder and kept for twenty-seven days at room temperature. Two attempts to pass through a Chamberland filter the agent causing the growth have been unsuccessful, but neither will withstand criticism on the technical side. The mucinous constituents of the growth even when much diluted rapidly clog such filters.

The growths which result from the injection of dried tissue or of a Berkefeld filtrate do not differ histologically from such as follow implantation of the living sarcoma cells, but they are late in appearing and a majority of them grow slowly. Many eventually metastasize, nevertheless, and lead to the death of the host. Tumors caused by the injection of a Berkefeld filtrate will themselves furnish material capable of causing tumors after suspension and filtration.

Character of the Agent.

Frequent attempts have been made to observe the agent causing the growth. Cultures from the living tissue remain sterile, so far as can be seen, even when made upon chicken blood-agar or upon media containing the unheated constituents of Plymouth Rock eggs. Stains, and the examination of fresh smears or of the filtrate with the dark-field microscope have likewise yielded a negative result. Whatever the causative agent, it is at or beyond the limits of visibility with the microscope. To conclude that we have to deal with a self-perpetuating parasitic organism is natural; but the facts can be well explained by supposing a chemical stimulant elaborated by the neoplastic cells, and capable of producing the disease in a new host, with, in consequence, a further elaboration of the same specific stimulant. However, no example can be cited in support of this hypothesis, whereas there are a number of diseases known to be caused by ultramicroscopic organisms.

Significance of the Findings.

The ultimate significance of these findings is hardly to be discussed at present. Perhaps all sarcomata, and even all carcinomata, will be found to depend, like the chicken tumor, on a causative agent separable from the cells. Or perhaps this tumor will remain unique in its etiology. Only the facts can decide. But there is an immediate significance to the findings that is obvious and considerable. Many of the characters of the malignant neoplasm have been taken to show that such diseases are dependent on disordered cell-metabolism, and while precipitated by external factors often, are otherwise independent of them. Yet here is a growth with just such characters, which can be produced in healthy individuals by the action of an agent derived from the neoplastic cells, in a sense self-perpetuating, and not improbably parasitic. It follows that the behavior of malign tumors can no longer be cited as evidence of their dependence on an intrinsic cell-derangement.

Discussion.

Dr. Beebe: These experiments are extremely interesting. I think we are not yet in a position to say what they mean. The fact that many experiments of this character have been tried with the other types of transplantable tumors, namely, those in rats, mice and dogs and have never given growth indicates that this tumor in the fowl stands in a class by itself. I believe that reports have appeared showing that the leukemia in fowls which is readily transferred may also be transmitted by cell-free filtrates. We are evidently dealing with a pathological process which is unique in character. It may be that the technique which has been employed in these other experiments has not been of the right type. Possibly the temperature or the reaction of the suspended medium has not been precisely right to preserve what may prove to be a fairly delicate mechanism in transmitting these growths, at least in cell-free filtrates.

If one is very strongly inclined toward the parasitic theory, it is possible to find in these experiments a satisfactory explanation of the process. It need hardly be said that such a position must be taken with a vast deal of care, for this tumor is unique in many respects, and as far as the experimental tumors are concerned, we have nothing that exactly corresponds with it in other species of animals. One of the most striking differences is the fact that this tumor shows metastases very early in its course while the tumors transplanted in other animals mestastasize comparatively late in their development.

I should be very much interested to know more about this matter than Dr. Rous has stated, probably more than he is now able or willing to say; for instance, the relation of temperature is one of importance. To what degree may these extracts be heated or cooled before the peculiar qualities are killed? Would it be possible to give inoculations of such heated or cooled extracts that in themselves would not produce tumor growth and yet that in themselves would not produce tumor growth and yet would produce immunity to a subsequent implantation of living tissue. The experiments are most interesting and suggestive and will stimulate cancer research in allied animal forms.

As regards the etiology of tumors in general, we are not yet able to do more than quote the facts that have been produced and not proceed too quickly to new theories.

Dr. I. Levin: I wish to say a few words in indirect support of Dr. Rous' work. I applied the exact techique of Dr. Rous' to a transplantable sarcoma of the white rat, and the results were uniformly negative. Consequently my filtrate of the sarcoma did not contain any cells and I may infer that Rous' filtrate does not contain any cells either. Apparently the tumor with which the Doctor is dealing may be propagated without the aid of the cells of the primary growth.

But the point that needs further corroboration is whether Dr. Rous induces in the new host the formation of a true metastasizing sarcoma or of multiple granulomata. I have shown a couple of years ago, that it is extremely difficult to differentiate these two conditions morphologically. It would be of great importance to investigate whether by some chemical or mechanical stimuli one could not induce the formation of similar multiple granulomata in the fowl.

Dr. Field: I would like to ask Dr. Rous some questions in regard to his use of filters. I have had a good deal of experience dealing with filters of one sort and another and I have not that faith in them that I had when I first started.

As I understood Dr. Rous, he made but one test as to the permeability of these filters and that was with regard to their preventing bacillus prodigiosus from passing through. Now, that is an exceeding large organism and a filter that might not allow the passage of this organism might be permeable to other organisms and especially to cells showing any degree of ameboid motion.

Another point, how long was the fluid in contact with the filter? In other words, how much time was allowed to pass the fluid through the wall of the filter, also under what pressure? It seems to me that these points should be thoroughly investigated before one draws any conclusions whatever. We all know that the mere passage of large quantities of fluids through any type of filter does not render them absolutely sterile though it certainly leaves only a minimum number of cells, and in regard to this point the comparative number of takes in injected fowl with the filtered and unfiltered materials ought to give one a clue.

Dr. MacCallum said that Dr. Rous' work seemed to have an especially striking relation to the various ideas which have been expressed in recent years as to the parasitic nature of tumor growths. Inasmuch as certain infectious diseases seem to depend upon an organism which, in some of its stages can be passed through a Berkefeld filter, the suggestiveness of the results is very striking.

It would be interesting, possibly, if Dr. Rous would attempt the stimulation of the growth of chicken tissue in vitro by the addition of some of this filtrate to the plasmatic media.

A CASE OF GASTRIC TETANY.*

DR. LARKIN.

Dr. Larkin expressed regret at not being able to present a complete record of the case as he had performed the autopsy the day before.

The patient was a hostler, forty-four years of age, and was taken ill two days before death. While occupied in a stable, he was seized with a sharp pain in the abdomen and when help arrived, was found stretched on the floor absolutely rigid. His head could be moved but the patient could not move his legs. He was semi-conscious. After three-quarters of an hour, the stiffness of the legs and arms relaxed somewhat. The patient refused to be taken to the hospital and remained in the stable until four or five o'clock in the afternoon when he was seized with another sharp pain in his stomach, vomited and passed again into a condition of general rigidity; his arms being gradually drawn up over his head and his legs becoming spastic. About eight o'clock he was again taken with a similar seizure, the third within a period of twelve hours, and in that condition was removed to St. Vincent's Hospital.

Dr. Stewart made the diagnosis of gastric tetany. Patient was pulseless, had very slow respiration, suffering from a great deal of respiratory oppression. After his entry into the hospital the period of general spasticity of his abdomen and extremities was at times accompanied by severe pain. After four hours in the hospital, he again relaxed and during this period of relaxation his pulse became almost normal, the temperature sub-normal. The abdominal distress persisted during this period of relaxation; he became able to speak, but not intelligently, so that they were unable to obtain from him an accurate statement as to the previous duration of his illness. After six hours in the hospital, he was again seized with another and fatal attack, accompanied by great respiratory depression. After an hour and a quarter, there being no relaxation of the muscles, he died apparently from asphyxia.

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*Presented at the January meeting of the N. Y. Pathological Society.

The autopsy showed a condition perhaps familiar to only some of the persons present. The stomach contained 4½ liters of fluid. The musculature of the stomach is very much thickened, especially along the anterior border, although there is no evidence of change in the mucous membrane. This thickening was not due entirely to oedema but rather to muscular hypertrophy and increased connective tissue growth in the sub-mucosa. At the pyloric end of the stomach, there was an old ulcer which had led to very marked constriction of the pyloric opening. The oesphagus was longer than normal and the position of the stomach in the body was not the normal one. Adhesions to the transverse colon and a long band from the great omentum to the tip of the bladder pulled the stomach over from its ordinary position. The parathyroid glands in this case had not yet been dissected out and Dr. Larkin said that if they were found to show lesions, he would report upon them at a later date.

PRIMARY LYMPHOSARCOMA OF THE STOMACH.

DR. LARKIN.

Dr. Larkin presented a case of lymphosarcoma of the stomach with lymphocytosis. The specimen was from a man fifty-four years of age, who had been under observation for a period of two months. Previous history was that of secondary anaemia, which had been progressive. There had been numerous blood examinations and before entering the Post-Graduate Hospital, the diagnosis of Leukaemia had been made, but was subsequently nullified. The symptoms at that time were those of an advanced secondary anaemia. The first evidence of local disease was a sharp pain in the epigrastric region, which from time to time grew worse, but there was no vomiting throughout the illness. About ten days before death, which occurred rather suddenly, a small lump appeared in the neck and another lump in the inguinal region on the left side. The glandular enlargement in the neck was removed and showed microscopically an ordinary lymphatic hyperplasia.

After having been in the hospital two months, the patient while going to the lavatory was seized with sharp pain. The next morning the abdomen became markedly distended. There was frequent vomiting and watery stools which were tinged with fresh blood. He died twelve hours after the beginning of his sharp pain.

The specimen presented is unusual. Looking into the stomach, one finds a very large ulcer which is perforated posteriorly into the lesser peritoneal sac. Along the greater curvature of the stomach there is found a flatter ulceration, the base of which is hard and about which the mucous membrane is raised. There are other depressions further back, as well as some smaller masses. If one compares the anterior border of the stomach with this large area, one finds great thickening of the mucous membrane. There is adhesion of the posterior part of the stomach with the pancreas which is equally involved in the growth. There is enlargement of the post-aortic lymphatic chain as far as the pelvis, resulting in compression of the aorta. The spleen is the seat of numerous smaller and larger masses, some of which have begun to undergo necrosis. The mass in the pelvis, along the iliac vessels, gives the general picture of lymphoma or lymphosarcoma.

The character of the lymphnodes, stomach, metastasis in the liver and the tumor itself is identical microscopically, the predominating type of cell being the lymphocytic; but one finds also some pyramidal cells and, in places, a large amount of hyaline stroma. The specimen is of some rarity, because of the position of the tumor.

DISSECTING ANEURISM OF THE AORTA.

CYRUS FIELD, M.D.

Dr. Field presented a specimen from a case of a colored man, 68 years of age, who entered Bellevue Hospital in the service of Dr. Alexander Lambert and died with a diagnosis of broncho-pneumonia and probable malignant endocarditis. The interesting feature of the case relates to the aorta.

On opening what was first taken to be the aorta, it was found that one entered a large arterial trunk lying to the right of the true aorta, and running parallel with it to its bifurcation. It was thought at first that one might be dealing with a case of double aorta; but further dissection showed that it was a dissecting aneurism. At a point in the aorta 2 cm. below the right subclavian, there is a circular opening 2 cm. in diameter in the aortic wall, leading into an aneurysmal tube, the internal surface of which is perfectly smooth and glistening, and which has the appearance of a large arterial trunk. Passing downward, the tube divides and follows both common iliacs, and the external iliacs beyond the inguinal canal. The right renal artery is given off from the true aorta; as it passes through the aneurysmal sac a portion of its wall has been eroded, so that there is an opening from the sac into this renal artery. The right kidney, therefore, derives its blood from both the circulation in the aneurysmal sac and the circulation in the aorta. That there was a free circulation within the aneurysmal system is shown by the absence of clot either in the main trunk of the aneurysmal sac or in any of its branches.

During life the patient gave no symptoms referable to such condition. It is interesting to note that in this case the Wasserman reaction was negative.

Discussion.

Dr. MacCallum showed some drawings to illustrate dissecting aneurisms, one of which was very similar indeed to the one shown by Dr. Field.

PRESENTATION OF SPECIMENS.

J. H. LARKIN, M.D.

Lipoma of Pleural Cavity.

I have two interesting specimens to present to the Society. The first one is a rather unusual case of tumor of the pleural cavity, a Lipoma. The patient was a man about 54 years of age, who had a number of sinuses around the rectum for which he had been operated on several times—in the Mount Sinai Hospital, in the New York Hospital and in Bellevue Hospital; he finally arrived at St. Francis Hospital, where he was operated on again and where he remained for a period of about two months. There were a number of deep sinuses and old scars of former operations, and with a probe one could pass readily down through the sinus far into the glutei, so that there was a constant absorption of pus and a constant febrile temperature for the period during which he was in the hospital. He finally grew markedly emaciated and died. The condition at the time of autopsy was rather interesting. After removing the chest wall it was found that the left lung overlapped the right, so that the entire anterior mediastinum could not be seen. Thinking that perhaps fluid had pressed the lung over on the left side, I put my hand down, and in doing so found no fluid, but a tumor which lay in the pleural cavity.

The tumor after hardening does not present the size that it did on removal. It is a lobulated mass, which flanges over the diaphragm along the line of its attachment to the ribs. The appearance is typically that of a lipoma, and this diagnosis is confirmed by microscopic examination. It does not, however, give the appearance of ordinary fat, but is a more solid mass, the capsule of which is traversed by small blood vessels.

The tumor is not so very interesting as a lipoma, because lipomata are of frequent occurrence. My experience with lipomata in general has been limited mostly to those occurring within the abdominal cavity. I have records of two or three lipomata in the gastro-colic omenum. They are very large and cause a great deal of disturbance. But I have at least, in looking over my notes, two cases of lipomata of the retroperitoneal region around the aorta in the neighborhood of the cœliac axis. In going over the literature of tumors of the diaphragm, I have been able to find the record of but one case of lipoma of the diaphragm. That is a case which was published by Stricker in a small memorial, which was afterwards published in one of the early editions of Virchow's Archives. That is the only reference I can find of a lipoma of the diaphragm. In fact, in looking over the literature for tumors of the diaphragm, one is amazed at the rarity of tumors in this part of the body. The tumor that is reported by Stricker is more of a microscopic find. He gives the dimensions of the tumor as measuring about 2 cm. in diameter. The microscopic examination proved it to be a strictly fatty tumor.

A Case of Ludwig's Angina.

This specimen was taken from a doctor on one of the Italian liners. He was a man of about 155 pounds, and was said by his brother surgeons to have been perfectly well until about three days after leaving the Italian shore, when he began to have sore throat. This condition became rapidly worse, in spite of treatment. They had noticed that there was œdema of the glottis and of the soft tissues of the pharnyx; and after four days the condition of the individual had become so serious that tracheotomy was performed; this seemed to relieve him at first, but with the general swelling of the neck region and anterior part of the chest the respiration became markedly embarrassed, so that the tracheotomy seemed to fail. They then removed the tracheotomy tube and passed a long tube down to the bifurcation of the bronchi in the hope of giving him more air, and that seemed to relieve him more and more. As they were nearing New York the individual commenced to get more markedly disturbed, the œdema increased, and he died just as he was coming into the harbor.

At the autopsy the contour of the neck was entirely obscured, so great was the swelling. The swelling came up to the ears and œdematous, brawny indurated masses extended from what appeared to be his jaw down to both shoulders, stopping short just at the deltoid muscle, so that the contrast between his head and the upper part of his chest was truly remarkable. The specimen which I present here to-night was obtained with a great deal of difficulty; one can see that the tissues show more or less brawny induration. No foci of pus were present; even when we dissected well into the axilla there was no suppuration. There was simply a deep, brawny, hard indurated tissue. There is not so much exudative inflammation as one would expect to find in such a dire condition. There is a still persisting œdema of the glottis mostly on one side, but acting as a valve.

The specimen here presents all the evidences of an ordinary diffuse cellulitis of the upper part of the neck. The bacteriology of this specimen does not give us any definite clue. The ordinary streptococcus has been isolated from this specimen in pure culture. The etiology of the condition is somewhat mixed up and no particular organism has as yet been associated with this particular lesion. The specimen is rather an unusual one on account of the tremendous amount of swelling and also on account of the condition of diffuse cellular infiltration. The microscopic examination of parts of this tissue here shows the ordinary evidences of a diffuse cellulitis of the neck.

Discussion.

Dr. Pappenheimer asked Dr. Larkin, in reference to the first case presented, whether the fat cells were of the adult or embryonic type?

Dr. Larkin replied that they were mostly of the small embryonic type and not adult fat cells.

TWO CASES OF CARDIAC ANOMALIES.

OTTO SCHULTZE, M.D.

Cor triloculare bi-auriculare: Specimen was obtained from a child about four months old, of whom no history could be obtained. The heart has two auricles, which are completely separated one from the other, and a single ventricle giving origin to aorta and pulmonary artery, which are separated by a short septum derived from the one dividing the common arterial trunk into aorta and pulmonary artery. The lumen of the aorta is larger than that of the pulmonary artery. The brain was almost completely anemic and the lungs congested.

Cor triloculare bi-ventriculare: This specimen was obtained from a female, 22 years of age; 55 inches in length, weighing probably 75 pounds. She was well developed, and had a perfect form, with the exception that the lower limbs were of the male type. When the knees were brought together there was a larger space between the thighs and calves than in the normal female. There was hair upon the cheeks and a few upon the upper lip. Hair in axilla was very scanty. Hair on legs and about peritoneum and arms. Contour of neck and shoulders rectangular. Shoulders were small and rounded.

At autopsy the heart was found completely contracted. Trachea and bronchi were filled with blood. The source of the hemorrhage was traced to the right lung, on sectioning which the superior branch of the pulmonary artery, over one-half inch in width, presented a parietal thrombus with open lumen extending as far as the main trunk. The pulmonary artery and its branches were greatly enlarged—nearly three times the size of the aorta —and at the entrance to each lung there were large aneurysmal distentions which extended into the smaller branches. The main trunk of the pulmonary presented a thin wall, the branches numerous plaques yellowish in color and thickened, without infiltration of lime salts. The hemorrhage had evidently proceeded from the rupture of a branch of the pulmonary artery into the right bronchus. The heart was very much enlarged, the right ventricle and auricle being over three times the size of the left ventricle and auricle. There is a single auricle into which open superior and inferior vena cava, coronary sinus and right and left pulmonary veins. There is an indication of a septum between the mitral and tricuspid orifices.

The history of the case is as follows. The deceased was perfectly well, with the exception of dyspnœa on exertion. On leaving for work in the morning, she collapsed in the areaway of her home, with a copious hemorrhage from the mouth. It was stated that a year or so ago, while living in Chicago, she had been examined by a large number of doctors in a clinic, who told her that she had a musical heart.

STUDIES ON IMMUNITY IN CANCERS OF THE WHITE RAT: THE SIGNIFICANCE OF ATHREPSIA.*

I. LEVIN, M.D., AND M. J. SITTENFIELD, M.D.

(From the Department of Pathology of Columbia University.)

In a previous communication one of the present writers[1] indicated the fact that the result of tumor implantation is determined by two factors: first, whether or not the implanted tumor becomes ingrafted; and, second, on the rate of its growth if ingrafted.

The mechanism of the ingrafting is common to tumor and to normal tissue. On the other hand, the ultimate fate and character of the graft depends on the rate of growth of the implanted tissue.

The rate of growth of an implanted tumor and with it the ultimate character of the tumor depends upon an interaction between the power of proliferation of the tumor cell and the resistance of the host. The mere grafting of the tumor is independent of the phenomenon of cancer immunity.

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*Conducted at the expense of the Geo. Crocker Special Research Fund.

[1] Levin, I.: *Journ. Exp. Med.*, 1910, xii, 594.

A great deal of confusion and controversy that exists in the attempted analysis of the results of the work on cancer immunity is caused by this lack of appreciation of the co-existence of the two factors determining the outcome of the tumor implantation. It seemed, therefore, desirable to undertake a revision of the work on cancer immunity.

The most popular and most generally accepted theory of cancer immunity is the one advanced by Ehrlich and commonly designated the *athrepsia* hypothesis. It is based on the following considerations:

Immunity or resistance of the host to the growth of an inoculable cancer is *not specific* in its character, and an animal immune against carcinoma will be also immune against sarcoma. The methods used to induce an artificial immunization are, likewise, not specific. When a cancer of low virulence is inoculated into and absorbed by the host, the latter is immune in the majority of cases against subsequent inoculation of any of the most virulent cancers. This non-specific character of cancer immunity Ehrlich designates by the name of *panimmunity*.

According to Ehrlich, as well as most of the investigators on the subject, an artificial immunity may be induced only by treatment with living cells. Growth of inoculated cancers, on the other hand, is also due to cell activity. Ehrlich contends that the growth of a cancer indicates that the tumor cells possess a great avidity for a certain specific food within the organism of the host. When cancer fails to grow, then either the organism of the host does not possess the necessary specific food or else the avidity of the cancer for this food is not strong enough to deprive the normal tissue cells of it. When the organism of the host is immunized by treatment with a cell emulsion, these cells bind the specific food, and consequently the cancer cells inoculated subsequently do not find the necessary nourishment and die. Immunity then to cancer growth consists in the lack of food-*athrepsia*.

The experimental evidence adduced by Ehrlich in support of his theory consists in the so-called *Zig-Zag Transplantations, second inoculation on a tumor bearing animal* and *inoculation of an emulsion consisting of two tumors* (carcinoma and sarcoma).

In the present investigation a separate detailed study was made of each of the above-mentioned experimental proofs, and in the following pages each of them will be considered separately. For the present investigation rats and mice were used, and in all five different tumors served for the experiments. Two of these were rat tumors; an extremely virulent Ehrlich sarcoma, and the Flexner-Jobling carcinoma which is not as virulent as the former. The three mice tumors used were Ehrlich's carcinoma of the mouse (No. 33), Bashford's carcinoma of the mouse (No. 27) and Ehrlich's sarcoma of the mouse. The last-named was the most virulent of the mice tumors.

PANIMMUNITY.

Ehrlich did not consider the phenomenon of panimmunity a direct proof of athrepsia, but there must undoubtedly be a certain relationship between the general non-specific character of the former and athrepsia, which is merely a phase in intracellular nutrition. Indeed, if athrepsia is to have a general application, it must be capable of explaining the conditions of panimmunity against the different tumors used in this research, and it may be stated that, in a general way, the fact of panimmunity was found to be correct for the majority of cases. But there were factors observed in the course of these experiments which cannot be explained on the basis of the theory of athrepsia. Of such experiments the following instances may be cited:

Experiment 1.—Twenty-nine rats which had been previously immunized against an inoculation of a rat carcinoma (Flexner-Jobling), were inoculated four weeks later with a rat sarcoma (Ehrlich); of these rats, 23 remained immune and only 6 rats, or 20 per cent. of the inoculated animals, grew the tumor, while of 20 control rats 17, or 85 per cent., took the tumor.

Of these two tumors the Flexner-Jobling carcinoma grows much slower than the Ehrlich rat sarcoma and does not reach so large a size. Consequently the former tumor has less avidity for the specific food than the sarcoma, and does not, according to the Ehrlich theory, use up all this food of the host. Therefore a sufficient amount of specific food should be left for the subsequently inoculated sarcoma cells, and it should be possible to inoculate the latter successfully in all the treated animals.

The following experiment shows again that all the facts of panimmunity cannot be explained on the basis of athrepsia:

Experiment 2.—Twenty rats were inoculated with a mouse sarcoma, and four weeks later when the grafts were completely absorbed were inoculated with a rat sarcoma. Of the 15 rats which survived at the last examination the tumor grew in only 2. This shows 13 per cent. takes, while in the 20 control animals the tumor took in 90 per cent.

It will be shown later that, according to the theory of athrepsia, the cells of a mouse tumor are unable to anchor the specific food of the rat. Consequently the specific food needed for the success of the inoculation of a rat sarcoma should exist in the same quantity in the rats treated with mouse sarcoma as in the control animals; still the rats treated with mouse tissue were immune to the inoculation of the rat tumor. The fact that it is possible to immunize a rat with mouse tissue and vice-versa was previously observed by Carl Lewin and by one of the present writers.

Another factor observed in the course of these experiments on panimmunity, which is of great importance in the consideration of the significance of athrepsia, consists in the following: whenever a tumor succeeds in growing in one of the previously treated animals, it attains the same size and virulence as in the control animals.

This phenomenon indicates that panimmunity with its nonspecific character is in reality an immunity to tissue grafting. On the other hand, when the cancer cells are ingrafted, such preliminary treatment of the animals with living tissue, as is used in experiments on panimmunity, does not exert any influence whatsoever on the subsequent growth or virulence of the developing tumor. The truth of this assertion is also evident from the fact that no immunization with living tissue is successful if it is done subsequently to the inoculation of the tumor.

The experiments of Rous[2] with inoculation of embryonic tissue show that by the same method an animal may be immunized against grafting of embryonic cells. The panimmunity is in reality an immunity against implantation of tissue. But since in all experimental cancer work with the inoculable tumors the first step always consists in the inoculation of a piece of the tumor, such tissue immunity obscures the actual immunity to the growth and development of the cancer.

Zig-Zag Transplantations.

This phenomenon which served as the main experimental basis for the formation of the theory of athrepsia consists in the following: When a mouse sarcoma is inoculated into a rat it grows there normally for about 8 or 10 days, then ceases to grow and is absorbed. But if before the absorption takes place the nodule is removed from the rat and transferred to a mouse, it continues to grow normally and may be subsequently transferred to another rat, where it will grow for about 8 days and so on.

Ehrlich explains the result of these experiments by the supposition that tumor cells, in order to proliferate, must obtain a certain specific food X, which they can find only in an animal of the same species as that from which the tumor cells have come. Cells of a mouse tumor inoculated into a rat proliferate for a few days, as long as the food X, which they brought over from the mouse, lasts. When this is used up, they do not find this specific food in the rat and cease to grow, but grow again when transferred to a mouse, where they find this specific food X. On the basis of this supposition Ehrlich created the general theory that whenever cancer cells fail to proliferate, it means that they fail to obtain the food X, either because the normal body cells have greater avidity to this food than the cancer cells, or else the cells with which the animals were immunized anchored all the specific food and the cancer cells inoculated subsequently could not obtain it.

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[2] Rous: *Journ. Exp. Med.*, 1910, xii, 344.

The experiments of Zig-Zag Transplantation were undertaken by the writers on all the tumors used in this investigation.

In the course of these experiments certain facts were observed which indicate that athrepsia cannot elucidate all the phenomena observed with Zig-Zag Transplantations.

The inoculation of the rat sarcoma and rat carcinoma into mice and of the Ehrlich's mouse carcinoma into rats uniformly produce small nodules in the host of different species. When these nodules were re-transferred into animals of the species, from which the original tumors were derived, for instance when a rat sarcoma was re-transplanted from a mouse into a rat, not a single good tumor growth could be produced by any of the three above-mentioned tumors.

With Ehrlich's mouse sarcoma and Bashford's mouse carcinoma the results of the experiments appeared to be more successful, *i. e.*, when a nodule of the mouse sarcoma or carcinoma after a sojourn of 8 to 10 days in a rat was removed and inoculated into a mouse, it grew in a certain number of cases into a good-sized tumor. The number of such successful inoculations, however, was much smaller than the number of takes in control animals, *i. e.*, in animals that were inoculated with tumor material which was taken directly from a mouse. While in the former the per cent. of takes was from 15 to 25, the tumors took in 90 per cent. in the control animals.

An analysis of these experiments on Zig-Zag Transplantations shows that all tumors, or at least all the tumors with which this investigation was conducted can be successfully grafted on the phylogenetically closely related animals, *i. e.*, from rat to mouse and vice-versa. The same holds true, according to Rous, for embryonic tissue. But the ingrafted cancer cells do not proliferate indefinitely and become malignant in the host of a foreign species. The explanation given by Ehrlich of this phenomenon does not seem to be adequate to explain all the factors in connection with it. If a mouse tumor fails to grow in the rat only for lack of specific food, then it should retain its normal virulence when re-transferred into a host of its own species. But experiments show that the virulence of a mouse or rat tumor is so diminished by its 8 to 10 days' sojourn in a host of a different species that it either fails to take at all when re-inoculated into a host of its own species, or else it takes in a very small percentage. It is evident, then, that the organism of the temporary host has a decided noxious affect upon the proliferating activities of the tumor cells; and, moreover, while the capacity for ingrafting in an animal of a foreign species is common to all the tumors studied, is non-specific, the amount of injury sustained through the sojourn in the foreign host is different with the different tumors.

SECOND INOCULATION ON A TUMOR BEARING ANIMAL.

Ehrlich maintains that animals on whom a successful inoculation of another tumor was previously made appeared to be immune against a subsequent inoculation, either of the same or another tumor. The opposite results found by Hertwig and Poll,[3] Gierke,[4] and Borrel,[5] he explains by the fact that in their experiments they used for the primary inoculations tumors of low virulence and slow growth, while in his experiments the animals received for the first inoculation an extremely virulent tumor. Only a very virulent rapidly growing tumor anchors all the specific food X, and consequently makes the successful take of the subsequently inoculated tumor impossible. A slow-growing tumor leaves a sufficient amount of the specific food for the successful take of a subsequent inoculation.

[3] HERTWIG AND POLL: *Abhand. d. K. preuss. Akad. d. Wissensch.*, 1907, I, *Abhand.* I.

[4] GIERKE: *Beitr. z. Path. Anat. u. z. allg. Path.*, 1908, xliii, 328.

[5] BORREL: *Bull. de l'Inst. Pasteur*, 1907, v, 207.

Experiments with a double inoculation were conducted with Flexner-Jobling rat carcinoma and Ehrlich's rat sarcoma. The latter is an extremely virulent and rapidly growing tumor and still a subsequent inoculation of the carcinoma was just as successful on an animal bearing a large sarcoma as the inoculation of the sarcoma on an animal with a growth of carcinoma. The most plausible explanation of the discrepancies in similar experiments of different investigators consists in the different behavior of the different tumor cells after a successful grafting. This latter factor is most evident in the series of experiments with an inoculation of an emulsion consisting of two tumors.

Inoculation of an Emulsion Consisting of Two Tumors.

Apolant inoculated an emulsion of a carcinoma and sarcoma into an animal and developed a mixed tumor showing the structure both of the carcinoma and sarcoma. If one of the tumors was originally more virulent than the other, or its virulence was increased artificially, then the resulting growth showed the structure of the more virulent tumor only. Ehrlich adduces the results of this experiment as another proof of the fact that the more virulent tumor cells obtain all the specific food of the host, causing the cells of the weaker tumor to die of starvation.

These experiments were repeated with two emulsions. One, consisting of the cells of Flexner-Jobling carcinoma and of Ehrlich's sarcoma of the rat, was injected into rats; and another, consisting of Bashford's carcinoma and Ehrlich's mouse sarcoma, was injected into mice. In both instances the sarcoma was a great deal more virulent than the carcinoma. The relationship in the virulence as between Flexner carcinoma and Ehrlich's sarcoma of the rat, and Bashford carcinoma and Ehrlich sarcoma of the mouse, is quite identical, but a most surprising difference was observed in the results of the two experiments. While in the rats on the injection of the emulsion there developed a mixed tumor, showing the structure both of carcinoma and sarcoma, the tumor in the mice appeared to be pure sarcoma.

Thus it seems that different tumors behave in a different manner when introduced simultaneously into an organism.

Of all the experiments stated above, the Zig-Zag Transplantations undoubtedly offer the best field for the analysis of the different phenomena of immunity in cancer. The apparent success of an inoculation of a mouse tumor into a rat may mean only the success of the initial grafting, since a rat possesses a congenital racial immunity against the growth of a mouse cancer. Indeed the nodule which develops in the rat upon an inoculation of a mouse tumor never develops into a large malignant growth. There is, consequently, a condition here, in which the dual character of the immunity to an inoculable tumor is perfectly apparent. The rat is susceptible to the grafting of a mouse sarcoma, but immune against its malignant development.

The success of the grafting of the inoculated cells undoubtedly depends upon conditions of nutrition. Thus *athrepsia* may serve to explain the conditions of resistance and susceptibility to the grafting of tumor, as well as tissue, cells. The formation of a highly vascularized stroma around the successfully ingrafted tissue and the lack of stroma formation in an unsuccessful graft (Russell[6]) also shows the importance of nutrition during this phase of the inoculation of a tumor.

On the other hand, the same experiments on Zig-Zag Transplantations clearly indicate that differences in nutrition cannot explain the reason why, in one successful tumor graft, a small nodule will form which is subsequently absorbed, while in another the nodule will grow into a large tumor and kill the animal.

As stated above, this investigation has shown that a lack of specific food alone cannot explain the failure of a mouse carcinoma or sarcoma to develop into a malignant *tumor* in the rat. The organism of the rat has a direct influence upon the mouse tumor, and its virulence is greatly diminished after a sojourn of a few days in this animal. The organism of the rat had, consequently, a noxious affect upon the proliferating activities of the cells of the mouse tumor. It is of great interest to note, in this connection, that upon an inoculation of these weakened cells into another generation of mice the normal virulence of the former returns. The following series of experiments illustrates this point:

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[6] RUSSELL: *Scientific Reports of the Imperial Cancer Research Fund*, 1908, No. 3, 341.

Experiment 3.—Twenty mice were inoculated with pieces of the Ehrlich mouse sarcoma taken from rats. Nineteen mice survived at the last examination, and of these one mouse took the tumor, which presents 5 per cent. of takes. The tumors from this mouse was inoculated in 20 other mice and the tumor took in 14 mice, or in 70 per cent.

It appears from these experiments that a mouse tumor through a sojourn in the rat reacquires the characteristics of a spontaneous tumor. Namely, it takes in a small percentage of inoculated animals, and this percentage increases in subsequent generations. But the diminution of the virulence of the tumor which takes place in the organism of the rat is due to congenital racial immunity of the latter. Furthermore, the immunity of the rat against mouse tumor is not due to conditions of nutrition, but is accompanied by an active noxious influence of the organism of the rat on the mouse tumor. Thus indirect evidence is brought forward through this investigation to show that immunity to cancer growth (but not to tumor grafting) is caused not by differences in intercellular nutrition, but by an active inhibitory influence of the organism of the host on the cancer cells. The search for direct evidence and the true nature of this inhibitory influence is the subject of our further studies on immunity in cancer of the white rat.

Discussion.

DR. ROUS: I have been somewhat interested in the subject of athreptic immunity, not directly, but indirectly through some experiments done for another purpose.

Some two years ago Gay, working for the Cancer Fund at Harvard, published a paper on Immunity to Cancer in which he divided the growth of cancer into two stages—one pre-metastatic, the other metastatic. He said that if, during the premetastatic period a second graft of tumor were made, the first tumor frequently retrogressed and the second usually failed to develop. Later, when metastasis was occurring, the course of the primary tumor was not affected by the second graft, and this, too, grew.

Interested by the work, I made some experiments which have not yet been reported. The Flexner-Jobling adeno-carcinoma of the rat was used, the same growth employed by Gay. My results do not confirm his. They give, however, some data on the subject of athreptic immunity. Here was a large, rapidly growing tumor and one could observe its influence on a second graft. But no influence was observed. Both in the period before metastasis and later, the second graft grew with the same rapidity as in the control animal. These observations form evidence against the current theory of athrepsia. In this connection it is to be remembered that when the primary tumor is very large, one is dealing with a sick, emaciated animal such as one would expect to find a poor host for new grafts. The failure of such grafts can certainly be explained from other points of view than that of athrepsia.

Dr. MacCallum was especially struck by the statement that the growth of pieces of mouse tumor, after a sojourn in a rat, when again transplanted to mice, showed a diminished percentage of "takes." This, if true, seemed distinctly opposed to the athrepsia idea. It might perhaps be thought that an explanation would be found in some fault of technique; but that seems hardly a valid objection, in view of the care that was taken in these experiments. The inoculation of mixed emulsions of tumors had certainly produced the most beautiful combinations of sarcoma and carcinoma.

THE EXHIBITION OF PHAGOCYTOSIS BY TUMOR CELLS.

F. M. HANES, M.D.

When the transplantable sarcomas and carcinomas of rats and mice are cultivated outside the body, the cells wander from the original piece of tissue by amœboid movement. Although the amœboid movements of tumor cells growing in vitro are slower than those of the amœba, they yet show numerous pseudopods which enlarge and retract in typical fashion.

The wandering amœboid tumor cells show active phagocytosis. If carmine particles are placed in the plasma used for cultivating the tumors, the wandering tumor cells take up the carmine granules most actively. It is thus seen that metazoan fixed cells, when placed in a favorable environment for growth outside the body, behave like some protozoan cells, showing amœboid movement and phagocytosis.

Discussion.

Dr. MacCallum thought that care must be exercised in comparing the growth of tumors in vitro with those in the body, for it is quite conceivable that tissues from the benign tumor would show the same wandering or amœboid activity as those from malignant tumors.

The time during which one can observe the characteristics of growth of tumor cells in vitro is so short that it hardly gives us an opportunity to observe the development of the peculiarities of malignant tumors. We have still, as the chief problem, the explanation of the difference inherent in the cells which gives them their enormous energy of growth, quite in contrast with that of normal cells.

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DR. W. G. MACCALLUM, *President.*

Through an error on the part of the Editor, the closing discussion of Dr. Rouse upon his paper—"A Sarcoma transmitted by an Agent Separable from the Tumor Cells"—was omitted from Vol. XI, Nos. 1 and 2, and is therefore included in the present number.

Discussion:

A SARCOMA TRANSMITTED BY AN AGENT SEPARABLE FROM THE TUMOR CELLS.

PEYTON ROUS, M.D.

DR. ROUS replying, said with reference to Dr. Field's remarks on the permeability of Berkefield filters, that these filters are undoubtedly often faulty, but that the evidence for an agent separable from the sarcoma cells does not rest upon its filterability alone. As already mentioned, the growth has been produced by means of material dried to a powder and kept in that form for many days—a procedure which kills the cells of warm-blooded animals, including tumor-cells, as experiment has repeatedly shown. Leaving this aside, Dr. Rous could not agree with Dr. Field's contention that the size of *Bacillus prodigiosus* was such as to make it in any way comparable with tissue cells in filterability. New Berkefeld filters (N) were used and filtration hastened by means of the suction pump. Filtration was never continued for more than an hour, at the end of which time, as a rule, only 10 to 30 cc. of fluid had passed through.

It was suggested by Dr. Levin that the growth might be a multiple granuloma, and he mentioned the difficulty in differentiating morphologically some of these forms from the true tumors. But the diagnosis of the growth rests to an inconsiderable degree on its morphological characters, though these are characteristic of the sarcomata. Its method of dissemination and its behavior on transmission are of the sort which distinguish the true neoplasms. That a growth with such features should be produced by an agent separable from the cells is the important point. The name given it is immaterial.

According to Dr. Beebe the growth is in many respects unique among tumors, and he cited in evidence the early occurrence of metastasis from it. In the paper the fact was perhaps not made clear that the occurrence of metastasis is only early in point of actual time involved. When the malignancy of the growth and its rapid development at the site of inoculation are considered, it becomes evident that metastasis takes place at relatively the same period as from mammalian tumors. Not until the primary growth has been present some time, and has attained a good size, are secondaries ever found.

Though it is true, as Dr. Beebe pointed out, that no single transmissible neoplasm heretofore studied corresponds with the chicken tumor at all points in its behavior, yet the latter conforms absolutely to the type, to the composite picture of the malignant neoplasm derived from the study of many individual and often widely differing tumors. The chicken sarcoma is perhaps unique in its close conformity to this picture at so many of its points, but in only one other respect, namely, in that there can be separated from its cells an agent which will produce the disease in new hosts.

When the sarcomatous tissue is heated to 55° C. for 15 min. it fails to cause the growth on implantation. Data on the resistance of the tumor cells and of the agent separable from them are now being collected.

HAEMANGIOMA INVOLVING THE SWEAT GLANDS.

JAMES CORSCADEN, M.D.

A tumor of typical warty vascular appearance was noticed at birth in a female child of four months. Within the few weeks preceding its removal there was very rapid growth. The tumor was in the lumbar region, five cm. from the mid-line and measured two by one cm. There was a similar growth the size of a pinhead on the buttock. On section the tumor appears as a very fine spongy network and is circumscribed.

Microscopically, there is a multilobular formation, the lobules being separated by dense connective tissue. The tumor is separated from the skin by dense connective tissue, and is bounded laterally and on its deep surface by fat. There is no distinct capsule. The tumor is composed of closely massed capillary spaces lined by large high endothelium in which occasional mitotic figures are seen. Near the skin the spaces are dilated and lined by flatter cells. Surrounding the endothelium is a thin layer of connective tissue, but no muscle. No transition from adjacent capillaries into those of the tumor is seen.

In most of the lobules are contained sweat glands intimately involved by the tumor tissue. There is no other connective tissue between the capillaries and the glands. No glands are seen in the interlobular connective tissue. The glands are never compressed and seem to be distorted only by the volume of tissue between the tubules. They do not have the appearance of having been pushed aside by the growing tumor.

Interest in the specimen lies in the bearing of the contained glands on the theories of origin of the tumor. The relation of the vascular tissue to the glands makes it apparent that the growth is one of the blood vessels normally disposed about the sweat glands, there being in no section evidence of compression or displacement of the glands by a growing tumor.

Ribbert, in his injection experiments, claims independence of the tumor blood spaces from the adjacent capillaries, and explains the occasional finding of normal independent structures in the tumor mass by saying that these are remnants of the tissues pushed aside by the growing tumor.

Albrecht employed the term Hamartoma for those enlargements of normal tissues due to excess of growth, abnormal arrangement or irregular position. Under this head vascular naevus is included by Trappe. The evidence presented by the present tumor points to the latter theory.

Discussion:

Dr. E. Moschowitz: In examining sections of liver angiomata in the aged, Dr. Moschowitz noted that at the periphery of these tumors, bile ducts could be frequently found in the fibrous walls of the veins of capsule. It occurred to him that the growth of these angiomata could be, possibly at least, accounted for by the incorporation of the normal hepatic veins in Glisson's capsule by a process of atrophy of the intervening tissue—a process incident to old age. He assumed that the accompanying bile duct and artery became obliterated and that the cavernous structure peculiar to the older and interior portions of the angioma was due to the breaking down of the walls of the hepatic veins due to pressure. In order to determine this, he cut a number of these angiomata serially and found undoubted evidence that at the periphery, at least, the normal hepatic veins formed part of the angioma. This observation, however, left the matter in the position of stale-mate, so to speak, because it was impossible to determine whether this phenomenon was really the result of liver atrophy, or the result of the normal growth of the angioma and consequent incorporation of the neighboring capsules of Glisson.

EXTENSIVE IRREGULAR NECROSIS OF THE LIVER IN AN INFANT.

C. W. FIELD, M.D., AND A. M. PAPPENHEIMER, M.D.

The liver which we wish to demonstrate was obtained at autopsy from an eighteen-day-old infant. The baby was one of twins born at eight months. Labor was simple, the puerperium uncomplicated.

The infant was well until the sixth day, when it refused the breast, and had to be fed with a medicine dropper. On the following day, it became slightly icteric and oedema developed about the feet. The oedema during the following days decreased; then reappeared, extending gradually to above the navel. There was also transient oedema of the face. The icterus diminished gradually, and disappeared entirely before death, but spasmodic twitchings developed and the child passed into coma, in which it died on the twelfth day of its illness.

The twin child was perfectly well until the seventh day. Then it too suddenly became unable to nurse, and developed oedema, and progressive icterus. A diminution in the amount of urine was noted, but no examination was made. The child died after four days and no autopsy was obtained.

The autopsy on the first child, which was held eighteen hours post-mortem, showed besides the lesions in the liver, double broncho-pneumonia and suppurative inflammation of the left mastoid. The appearance of the liver was striking. The organ was about normal in size, the surface was smooth, the edge sharp, the consistence somewhat firmer than normal. The whole organ, both on the surface and on the cut section, showed a peculiar mottling—irregular areas of a greenish gray, slightly translucent appearance, alternating with reddish and yellowish red areas. The grayish areas, which were found subsequently to represent intact liver tissue, were slightly more prominent above the surface than the reddish portions.

They were sharply circumscribed, and on close inspection it could be seen that they were in relation to, and formed irregular mantles about, the larger portal spaces.

The mottled appearance observed in the gross is even more striking and distinct in the stained sections. Here one may discern sharply demarcated, irregular islands staining more deeply than the surrounding tissue and corresponding, under the microscope, to areas of well preserved liver cells. By far the greater portion of the liver, however, is composed of liver cells which have undergone regressive changes.

In sections stained in hematoxylon-eosin, the degenerated areas show no trace of lobular structure. The individual cells no longer show a columnar arrangement but are irregularly disposed and separated one from another. The degenerated cells are distinctly smaller than the normal cells. The protoplasmic outline is often indefinite. The cytoplasm of the affected cells does not take up the hematoxylon but shows a strong affinity for the eosin. With the immersion, the protoplasm has a foamy, vacuolated structure and in frozen fixed sections the cells are found filled with smaller and larger droplets staining bright orange red, with Sudan III. Nowhere, however, are there seen larger globules completely filling the cells and compressing the nucleus.

When treated by the Ciaccio method for the demonstration of the more complex lipoids, the degenerated cells show numerous droplets staining a dirty brownish yellow with Sudan III. Free flat globules are also found in small numbers within the capillaries. The nuclei are shrunken in comparison with that of the normal cells, approximately not more than half the size. They are circular in outline and stain densely and diffusely. Occasionally they are in the form of irregular, pycnotic fragments lying at the periphery of the cells; occasionally also signet and crescent forms are seen. Some of the cells appear to have lost their nucleus altogether, although this may be due to the fact that the nucleus lies without the plane of the section.

The islands of unaffected liver cells form irregular mantles about the larger portal spaces and are also preserved in places as a thin layer just beneath the serosa. All the portal spaces, however, are not surrounded by normal liver cells. In general the islands of normal cells preserve their characteristic lobular structure and radial arrangement about the central vein. The individual cells are approximately of normal size, showing no hypertrophy when compared with cells from the normal liver of an infant of approximately the same age.

No fat globules or glycogen are present, but in the Ciaccio preparation many of the normal cells show a diffuse reddish brown discoloration. The capillaries in the normal areas are distended with well preserved blood cells. Here and there are found small groups of cells which under the immersion can be identified as normoblasts and megaloblasts. Large cells with a vesicular nucleus and somewhat more basophilic cells, probably representing precursors of the megaloblasts, are also found. In a few of the megaloblasts, karyokinetic figures were seen. These erythoblastic centers, which were studied in Giemsa-stained sections, are seen not only in the capillaries of the normal liver tissue but also in the degenerated areas. Moreover, nucleated red cells of all types are present in unusual numbers throughout the liver. There is, therefore, an active hemopoesis, apparently unaffected by the degeneration of the parenchymal elements.

There is very little fibrosis or evidence of active connective tissue hyperplasia. Some of the smaller vessels in the periphery of the lobules are surrounded by apparently actively growing fibroblasts, and in the neighborhood of the large portal trunks the connective tissue of Glisson's capsule is somewhat more abundant than normal. With Bielschowsky's stain no increase in the intralobular connective tissue is apparent either in the normal or the degenerated regions.

There is in many places evidence of regenerative activity on the part of the smaller bile ducts. From the periphery of the lobules we see small ingrowths of cells with dark staining protoplasm containing various numbers of irregularly-sized vesicular nuclei, some of which are in active karyokinesis. Three mitotic figures were seen in a single mass of cells. The direct connection of these cell masses with the bile ducts in the portal spaces and at the periphery of the lobules can in some places be demonstrated in serial sections. The bile ducts give off lateral off-shoots which soon lose their lumen, branch, and penetrate the periphery of the lobules for a short distance. The cells are no longer cylindrical but irregularly polygonal, and tend to lie in double rows, though the terminations of the sprouts may be three or four cells in thickness.

Owing to the methods of fixation employed, no bile can be demonstrated in these new formed cells; neither do they contain fat in appreciable amount, or glycogen. The efforts at regeneration displayed by the intact liver cells are negligeable. A rare mitosis is found, but there is no reduplication of the cells of the liver cords, no loss of the radial arrangement, no formation of large multinuclear cells and no ingrowth of new formed cells into the degenerated lobules. This is probably due to the short course of the disease, affording no time for the development of the adenomatous hyperplasia described by Meder,[1] Marchand,[2] Stroebe,[3] MacCallum[4] and others in long standing cases of liver atrophy. Regeneration, in this case, therefore, is practically limited to the solid sprouts derived from the interlobular bile passages. Active and conspicuous as is this proliferation, it is not probable that it has in this case led to the regeneration of functional liver cells. The terminal solid buds resemble liver cells in the appearance of their nuclei, but the cells do not assume a characteristic polygonal shape of normal liver cells, nor do they enter into a characteristic arrangement with the persistent capillaries. Furthermore, regressive changes may occasionally be noted in the nuclei of the terminal cells of the sprouts, showing that some at least of the new formed cells are short lived.

Very striking and significant is the absence of acute inflammatory changes. There is no accumulation of small, round cells in the portal spaces, no infiltration of polynuclears. Neither can there be observed the phagocytosis of necrotic cell detritus by the desquamated endothelial cells of the capillaries as described in cases of focal necrosis by Mallory. These features are opposed to the idea of a direct bacterial causation for the necrosis.

As in so many of the reported cases of acute atrophy of the liver, we are quite in the dark as to the real cause of the lesion. The finding of slight cirrhotic changes in the pancreas, together with rudimentary islands of Langerhans (some of which apparently show a direct connection with the pancreatic ducts) suggested syphilis as a possible factor. Syphilis has been brought into relation with acute yellow atrophy by a number of observers. Meder in 1895 was able to collect twenty such cases.

In the case here reported, no spirochetae were found in Levaditi sections from all the principal organs. This fact, together with the absence of other characteristic syphilitic lesions, seems sufficient to exclude syphilis as a positive causative factor.

Since attention has been called to necrotic lesions in the liver, occuring as a sequel to chloroform narcosis, it might be suspected that chloroform administered to the mother during labor might account for the lesion. We have, however, ascertained that no chloroform was used in this case. No cultures were made at the time of autopsy, so that we cannot say whether or not the liver lesion is a manifestation of a general bacterial infection. The absence of micro-organisms in the necrotic areas in sections stained by Gram, methylene-blue and Giemsa, as well as the lack of inflammatory reactive changes, seem against this possibility. The lesion represents evidently what we are accustomed to call a toxic necrosis; whether due to bacterial or metabolic toxins it is not possible to say.

Our study of the literature is still incomplete, but we have thus far been able to find but one reported case of extensive necrosis of the liver occuring in young infants. This is the case published by Aufrecht[5] in 1896. The mother was a girl 19 years of age, primipara. The labor was normal After twenty-four hours there was noticed in the child swelling about the feet, which on the second day extended above the symphysis. The swelling is described as hard, doughy and could be pitted on pressure. On the second day, also, there developed slight general icterus; the urine contained a small amount of albumin and "leucin spheres." On the third day the oedema extended to the navel and punctiform hemorrhages appeared on the left leg. The icterus increased. Death took place on the sixth day. At the autopsy, sixteen hours after death, aside from scattered petechial hemorrhages in the serous membranes, the lesions were confined to the liver. The organ is described as weighing 100 g., was firm, bluish black in color and showed no acinal markings. Microscopically there was complete loss of the lobular structure. The nuclei were shrunken and stained poorly. The cells were vacuolated. There was extensive hemorrhagic extravasation. Many bacilli were found in the capillaries.

Although the report of this case is somewhat incomplete, there seems to be a resemblance in the clinical history as well as the pathological findings.

Todt[6] in 1903 collected from the literature thirty-two cases of acute yellow atrophy in infants and young children. None of these, with the exception of the case above quoted, occurred in the new-born; almost all of them were similar clinically and pathologically to cases occurring in adult life. In conclusion, we wish to call attention to the resemblance between the lesions in the liver of our case, and those produced in dogs by Pearce[7] by injection of large doses of hemolytic serum. As is well-known, he attributed the necrosis in his experimental lesions, to "obstructive congestion of the capillaries and the smaller branches of the portal vein by fused masses of red cells." In our case, there was absolutely no histological evidence of such a condition, and we have no basis for considering the lesion as the result of infarction.

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[3] Stroebe: *Ziegler's Beiträge*, Bd. 21, 1897, S. 379.
[4] MacCallum, W. G.: *Johns Hopkins Mospital Reports*, Vol. 10, p. 69.
[5] Aufrecht: *Ctrllblt. f. Inu. Med.* No. 11, 1896.
[6] Todt: *Inaug. Diss*: Berlin, 1903.
[7] Pearce: *Jour. of Exp. Med.* Vol. 8, 1906, p. 64.

Discussion:

Dr. Pappenheimer: I think one of the peculiar faatures, which Dr. Field has not emphasized, is that there was no jaundice at the time of death, and only a slight amount during the course of the disease. The only explanation that we have been able to make for this curious fact is that in the degenerated portion, the destruction of the cells was so complete that there was practically no bile produced, while in the intact liver cells which presumably have their conducting mechanism intact, there was no reason for a stasis of bile. I believe there have been a few cases of acute atrophy of the liver in adults in which jaundice has not been marked.

ON ISO-AGGLUTINATION IN DOG'S BLOOD.

DRS. OTTENBERG, S. S. FRIEDMAN, AND D. J. KALISKI.

Recently two of us reported that normal iso-agglutination could be detected in the blood of rabbits and in the blood of steers.* We desire now to report one additional fact, viz.: the occurrence of iso-agglutination between the bloods of normal dogs.

Iso-agglutination of human blood has been known for about ten years. Ever since Landsteiner's work it has been known that all human beings can be divided sharply into four groups according to the agglutinative power of their blood serum for each other's blood cells. There are two iso-agglutinins and two corresponding iso-agglutinable substances. One group of human beings has in the blood serum both agglutinins, and in the blood cells no agglutinable substances (that is, the cells are not agglutinable). Another group of persons has the first agglutinin and the second agglutinable substance. The third group has the second agglutinin and the first agglutinable substance. The fourth group has both agglutinable substances and no agglutinin. These peculiarities are a permanent characteristic of the blood of each individual. Before this society, in 1908, in a paper with Dr. Epstein, I announced my belief that these characteristics were hereditary and were inherited according to Mendel's law. At that time I had examined only five families and could not definitely prove the point. Recently von Dungern and Hirschfeld have proved that human iso-agglutinable substance is hereditary according to Mendel's law. Von Dungern has also shown by the method of absorption that many of the hetero-agglutinins of animals' serum can be identified with one or the other of the human iso-aglutinins, and that many of the hetero-agglutinable substances of animals' red cells are closely similar to the iso-agglutinable substances of human blood. Actual iso-agglutination in lower animals has been overlooked, however, probably because most of the agglutinations are very weak and require a special technique for their demonstration.

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In a previous study on the quantitative relationships of agglutinative serum and agglutinable red cells it was found that an excess of cells absorbed a small amount of agglutinin without agglutination being visible at all. Therefore in the present studies the method used was that of mixing very large proportions of serum with very small proportions of red blood cells.

While natural iso-agglutinins had not been described before our work, immune iso-agglutinins had been developed in dogs by von Dungern and Hirschfeld. We have repeated their work and have developed immune iso-agglutinins in two out of six dogs injected. The mutual agglutinations of these six dogs are shown in chart I. Whether these immune agglutinins are exaggerations of the natural agglutinins which (with an improved technique) we subsequently discovered, we cannot state at present.

CHART I.

"Immunized' Dogs.

SERA.

		A	B	C	D	E	F
CELLS	B	—	—	+	+	—	—
	C	—	—	—	+	—	—
	D	—	—	—	—	—	—
	E	—	—	—	+	—	—
	F	—	—	—	—	—	—

In looking for normal iso-agglutination between the bloods of different dogs we were at first unsuccessful and only succeeded when we adopted for our technique the mixing of fifteen parts of serum with one part of defibrinated blood. (The ease with which dogs' cells laked in normal saline solution was one of the causes of failure in the early experiments.) The mixtures were made in capillary pipettes of two to five milimeters diameter, using a modified Wright technique (as described by Epstein and Ottenberg, Archives of Internal Medicine, May, 1905). The reason for the use of this technique was that the work could be done with small quantities of blood, and particularly that in the thin layer of dilute cell-suspension in a small pipette it was possible to see fine agglutination which escaped observation in ordinary test tubes.

There are many precautions that are necessary to get constant results. The glass tubes must be thoroughly cleaned and washed in distilled water, and dried. After the mixtures are made the open ends of the pipettes are sealed with paraffine to prevent drying. The mixtures are generally observed for one hour at room temperature. At the end of this time with dogs' blood, agglutination when it occurs can usually be seen. A column of fluid about one inch long is found most convenient, and it is important to have the air bubbles (which by rotation of the tube are used as mixers) of a uniform, rather small, size. All the tests reported here were made in duplicate, that is, two of us making independent readings found practically the same results. As stated above, the agglutination between the bloods of untreated dogs is feeble as compared with the iso-agglutination of human bloods or of immunised dogs. By thorough mixing the clumps can be made to disappear, but generally they form again if the mixture is allowed to stand.

Ten or twelve dogs were bled at a time, and their bloods tested against each other at once. As can be seen in the chart, the agglutinations which occur admit of a certain grouping, but, as in the case of rabbits' bloods, there are irregular agglutinations which do not fit well in the classification, and the groupings can therefore be regarded as only tentative. The one definite division of the bloods is into those whose serum is non-agglutinative and those whose serum agglutinates some other dog's cells. Agglutinability of the cells seems to be irregular. In general those animals whose sera agglutinate the cells of most of the other dogs have cells which are agglutinated by the sera of only a small number of the other dogs—and vice versa. Auto-agglutination was never observed, though it was tested for regularly.

CHART II.*

Dogs March 29

SERA.

		1	6	8	11	4	9	10	2	3	5	12
	1	—										
	6	+										
	8											
	11					+						
	4	+	+	+	+		+	+				
CELLS	9	+	+	+	+		—	+	—			
	10	+				+						
	2	+				+	—					
	3	+	+	+	+							
	5	+	+	+	+							
	12	+	+	+	+	+						

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* The heavily shaded lines represent a tentative grouping, although the authors do not believe that sharply defined groups, such as are found in human beings, exist in either dogs or rabbits.

Chart III.

Dogs April 22

SERA.

Cells	11	18	8	13	17	4	2	15	16	5	4	14
11				+		+			—			
18	+			—		+	—			—		—
8	+	—	—		—							—
13						+	—	—	—	—	—	—
17	—						—	—	—	—	—	—
4	+	+	—	—		—	—	—	—	—	—	—
2	—		—	—	—	+	—	—	—	—	—	—
15				—	+	+	—	—	—	—	—	—
16	—	—	—	—		+	—	—	—	—	—	—
5	+	+	+	—	—	—	—	—	—	—	—	—
9	+	+	+	—			—	—	—	—	—	—
14	+	—	—	—	—	+	—	—	—	—	—	—

As to the permanence of these peculiarities of dogs we can say little at present. Most of the tests were repeated with blood obtained after two or three days and were found to be unchanged. In a series of dogs (chart 3), examined on April 22 were six dogs which had been examined on March 29 (chart 2). In the meantime several of the dogs had been used in various transfusion experiments. It will be seen by direct comparison of the record of the six surviving dogs (chart 4), that only two new inter-agglutinations appeared, and only one of the former agglutinations was lost, out of thirty combinations. Whether these changes were due to the treatment which the dogs received, we are not at present prepared to say.

Chart IV.

Six Surviving Dogs
On April 22nd as compared with same dogs on March 29*

SERA.

(March 29th)

		8	11	4	9	2	5
Cells	8	—	—	—	—	—	—
	11	—	—	+	—	—	—
	4	+	+	—	+	—	—
	9	+	+	—	—	—	—
	2	—	—	+	—	—	—
	5	+	+	—	—	—	—

(April 22nd)

		8	11	4	9	2	5
Cells	8	—	+	—	—	—	—
	11	—	—	+	—	—	—
	4	—	+	—	—	—	—
	9	+	+	—	—	—	—
	2	—	—	+	—	—	—
	5	+	+	—	—	—	—

* Several of the dogs had been used in transfusion experiments in the interim.

Discussion:

Dr. Field: I must say very frankly that I would not trust the results obtained with such a method. In working with agglutinins, as with all immune bodies, one cannot be too careful. In the first place, in agglutination, the quality of the glass makes a great deal of difference. Unless one used glass tubes of the very best quality, which had been washed under known conditions most carefully and tested, one could not accept the results at all, because one may get curious results if the technique is not of the best.

Dr. Levin: Dr. Ottenberg's paper presents the results of a comparative study, and the faults of the technique, if there are any, are identical for all sets of experiments. The errors would consequently be neutralized on the analysis of the results.

If I understand Dr. Ottenberg correctly, the presence of agglutination is not constant in the dogs. The phenomenon may be present at a certain time and then disappear.

I should like to know whether there is a method by the aid of which we can change the phenomenon at will. For instance, if two dogs were tested, one immediately after and the other before a meal, whether the property of iso-agglutination of the serum would be different.

The second question is whether the blood serum of a dog possesses the property of homo-agglutination. The study of this property as indicating the inter-relationship between cells and bloodserum of the same animal, may be of some aid in the investigation of the pathogenesis of malignant tumors.

Dr. Ottenberg: In regard to Dr. Field's criticism, there is a certain amount of truth in what he says. Notice, however, in regard to these experiments that they have all been repeated with substantially the same results. Some of the irregularities may have been due to such causes as he suggests. The method is not ideal.

I have tried out the method pretty thoroughly in human iso-agglutination and hemolysis tests, of which we have done many hundreds in the past three years. With this method the results have always agreed with the well known peculiarities of human iso-agglutination, and when hemolysis occurred it could always be confirmed by repetition of the test. In these agglutinations in the blood of various animals, generally far more delicate than in the blood of human beings, we probably do make an occasional mistake. But on the whole the tests come out quite constant, and they control one another, so that we feel confident that the results are all right.

With regard to Dr. Levine's first question, auto-agglutination has been stated to occur in pernicious anemia. I have often looked for it myself, but have never found it. Probably what has been called agglutination in these cases is simply the clumpy appearance of any very anemic blood as it runs from the needle prick.

Landsteiner has indeed described auto-agglutination of normal human cells, but the highly artificial conditions of his experiment, which included bringing the mixtures down to the freezing point, render it highly improbable that the phenomenon which he observed have any relation to ordinary agglutination. As Landsteiner himself points out, auto-agglutinins, even if formed, would be extremely difficult, if not impossible to demonstrate, because being always in the presence of a large number of susceptible cells, the agglutinins would be absorbed as rapidly as formed.

With regard to Dr. Levine's second question, the only methods that I know of changing these properties in the living animal are by immunisation or by absorption. Immunisation I have already referred to. I recently saw a human blood transfusion which illustrated this absorption of agglutinin *in vivo*. Before the transfusion the patient's serum was agglutinative to the donor's cells, but not the donor's serum to the patient's cells. Serum obtained from the patient after the transfusion no longer agglutinated the donor's cells; all the agglutinin had been absorbed by the donor's transfused cells. On the other hand the patient's blood cells collected after the blood transfusion were agglutinated by his own serum saved from before the transfusion (because, of course, the patient's cells after the transfusion consisted largely of donor's cells, susceptible to patient's original agglutinin). These conditions persisted for several days in this case.

Human iso-agglutination seems to vary in intensity from time to time, but there are no accurate studies on this question, and the causes of the variation are unknown. (I can add from recent work with Dr. Friedman that rabbits' iso-agglutinins seem to be far less constant than those of dogs or human beings.)

THE FORMATION OF METASTASES AFTER AN INTRAVASCULAR INJECTION OF TUMOR EMULSIONS.

I. LEVIN, M.D., AND M. J. SITTENFIELD, M.D.

(From the Department of Pathology of Columbia University, New York.)

(George Crocker Special Research Fund.)

It is generally accepted that metastasis in malignant tumors is formed by the proliferation of the tumor cells which have been transported to distant parts of the organism through the blood or lymph channels. The cells of the primary tumor penetrate in some manner into the lumen of the vessels, are swept away by currents as emboli, and finding lodgment in some distant part of the organism, they proliferate and form secondary tumors.

This conception of the formation of metastasis was established through observation of autopsy material and no direct experimental proof of the matter was adduced up to the present. All experiments with intravascular injection of human tumor material into animals either gave negative results or were entirely untrustworthy.

In all the extensive literature of the last decade on the subject of the transplantable cancer of the white mouse and rat there appears no statement in regard to intravascular injection of tumor material with the aim of forming metastasis. The only exception is a short note by Graf, who obtained negative results.

Metastasis in malignant tumors of the white mouse and rat occurs rarely as compared with human cancer, and the channels for the transportation of the tumor cells are in the majority of cases the blood vessels. The reason for the rare occurrence of metastasis in the rat and mouse, Ehrlich, in accordance with his athreptic theory of immunity, sees in the fact that tumors in these animals are usually of extreme malignancy and grow to very large size. The cells of the primary tumor use up all the specific food found in the organism of the host, and the cells transported from the primary tumor to other regions of the organism do not find the necessary nourishment and consequently cannot proliferate. Carl Lewin, on the other hand, thinks that the fact that metastasis in these animals takes place only through the aid of the blood vessels and not the lymphatics, accounts for the rare occurrence of metastasis in these animals. As was shown by M. B. Schmidt through his observations on human cancer, blood is capable in majority of cases of destroying cancer cells, found within the blood vessels.

The study of the influence of the blood upon the cancer cells carried by it and of the capacity of such cells to form metastasis may serve to clear up a number of phenomena in the genesis of cancer. In view of this a systematic study was undertaken by the writers on the experimental formation of metastasis, of which the present communication forms the first report.

The experiments consisted in an injection of a tumor emulsion into the jugular vein or carotid artery of a white rat, and were conducted on three different tumors.

Sarcoma of the white rat.—This tumor is very malignant, grows to a large size, and the occurrence of metastasis after a subcutaneous inoculation is very rare. In hundreds of animals inoculated by the writers, local dissemination was observed not more than in a half dozen cases, and once only was metastasis found in the liver. An emulsion of this tumor was prepared by cutting it in Haaland's mincing machine, grinding in normal salt solution and filtering through a layer of coarse gauze. The milky opalescent fluid contains a sufficient number of living cells to produce a tumor growth upon a subcutaneous inoculation. Thirty-six rats received an injection of this emulsion into the jugular vein. The animals were killed at periods ranging from eight days to four weeks after the injection and a thorough search made in all the organs for metastasis. Not in a single instance was a metastatic tumor found. No microscopical study was made of the organs which appeared normal on gross inspection, since this investigation does not concern itself with the question, where the tumor cells circulating in the blood find lodgment, but whether such a cell transported into a certain organ will form there a visible metastasis. All suspicious nodules found anywhere and all lungs appearing abnormal on gross inspection were examined microscopically with negative results. The same negative results were obtained in six rats, where the injection was made into the carotid artery, and the animals survived. This method is very difficult of execution and the animals usually die a few minutes after the injection from respiratory paralysis, while the heart continues its action a few minutes longer.

Carcinoma of the white rat.—(Flexner-Jobling.) This tumor is not as malignant as the previous one, but metastasis occurs frequently after a subcutaneous inoculation. The metastasis is usually found in the lungs, the heart and even in the lymphatic glands, though the authors believe that in most cases the metastasis were produced through the blood current. Sixteen rats received an injection of an emulsion of this tumor into the jugular vein. In three animals metastasis was found in the lungs; no other organ showed any metastasis. Six rats survived an injection into the carotid, and of these animals one showed metastasis in the lungs. In another rat, in which the injection was made in the carotid against the stream of blood, the animal was found dead twelve days later. At the autopsy a nodule was found on the wall of the left ventricle. The animal remained dead in the cage over night, and the specimen had greatly deteriorated, still the nodule resembled microscopically the picture described by Flexner and Jobling for a metastasis found by them in the heart.

Sarcoma of the white mouse.—Ehrlich has shown that when this tumor is inoculated subcutaneously into a rat, there forms a small nodule, which remains for eight to ten days, and is then absorbed. No metastasis formation of this mouse tumor into a rat were ever noted. An emulsion of this tumor was injected into the jugular vein of twelve rats. The rats were killed in periods of four to eight days, and in two of the animals metastatic nodules were found in the liver. Neither in the lungs nor in any other organ was there found any metastasis.

The results of these experiments seem to indicate, in accordance with the opinion of M. B. Schmidt, that cancer cells introduced into the blood circulation in a majority of cases lose their proliferating power. Ehrlich's opinion that the most virulent tumors do not form metastasis also seems to be correct, as no metastasis was formed upon the injection of the most virulent sarcoma of the rat. But the athreptic theory does not explain this fact. None of the animals had any sarcoma growth anywhere, and consequently the sarcoma cells introduced into the circulation could find all the necessary specific food.

The most interesting phenomenon observed in the course of these experiments consists of the fact that, while the Flexner tumor found lodgment upon an intravascular injection in the lungs, the mouse sarcoma produced metastasis only in the liver. It would seem that the different topographic distribution of metastasis in the different kinds of malignant tumors is due not so much to the difference in the channels through which the cancer cells are transported, and which were identical in all experiments reported here, but to a specific affinity between cancer cells and cells of certain organs. The comprehension of this specific affinity between a cancer cell and a particular part of the organism of the host may be helpful in elucidating many factors in the genesis of tumors and will be the main object of the further study of the experimental metastasis formation by the writers.

Discussion:

Dr. Moschcowitz thought that the paper of Dr. Levin was highly suggestive, but it did not explain why the involvement of lymphatics in carcinoma was nearly always reginal, nor could it explain such phenomena as retrograde lymphatic involvement. According to Dr. Levin, involvement of lymphatics would be a haphazard affair, and would not occur with the regional precision that it does.

Dr. Larkin: Goldman and Schmidt's research in cancer cells is a very interesting piece of work. I doubt, however, if the Goldman and Schmidt observations are universally concurred in. However, the mode of transportation of cancer cells, after all, is not of so very much importance in the formation of a metastasis as the factor that causes cell growth after it goes from an apparent focus to a distant part. This is something which in pathology we are always interested in.

However, Dr. Levin's presentation of the theory of Goldman and Schmidt was quite accurate indeed, and deserves a great deal of consideration in the elucidation of this problem of metastasis.

Dr. Pappenheimer: I would ask Dr. Levin if any experiments have been made with the direct injection of cancer extracts into different organs—and if by that method the organs show the same selective affinity for a given tumor as they do with the intravenous injection.

Dr. Levin: Neither Goldman nor Schmidt, much less myself, claim that blood vessels are the only channels of transportation of metastasis. There is no question that cancer cells may travel through lymphatics. The researches of Goldman and Schmidt are of great importance mainly for the reason that they indicate that the same channels may serve for the transportation of all kinds of tumors. The difference in the localization and character of metastatic tumors is due only to the difference in the affinity between organ cells and tumor cells.

To answer Dr. Pappenheimer, I may state that inoculations into parenchymatous organs, while presenting a number of interesting phenomena, do not help in the elucidation of the question of formation of metastasis.

DEMONSTRATION OF SPECIMEN: CHORIO-EPITHELIOMA OF THE UTERUS.

J. G. HOPKINS, M.D.

The patient was a woman of 33 years, who in last July was delivered of a six months infant which died shortly after birth. Past history was practically negative, there having been no illness since childhood, but a few weeks before delivery she had had some metrorrhagia and after delivery she continued to bleed and lost weight and strength. There was no examination made of the placenta at the time of miscarriage and we were unable to find out anything about its condition. She grew progressively weaker, and had one or two attacks of syncope. On September 11 she was admitted to the Sloane Hospital for Women on Dr. Cragin's service. She at that time had a cough with bloody expectoration which had already been present for two or three weeks. There was one nodule palpable in the vagina. On account of the evidence of quite extensive metastasis no operative interference was attempted. On October 3 she died, three months after delivery. From the time of admission she had a fever of a septic type, at one time as high as 105°.

At autopsy the uterus contained in the posterior wall a soft and necrotic mass, which extended out and penetrated the uterine muscle at the lower portion of the cul de sac. It also extended out through the broad ligament on one side and the uterosacral ligament on the other. There were three nodules in the vaginal wall. The lungs presented the striking and characteristic appearance often found in these cases; they were studded with hemorrhagic nodules from 0.3 to 2 cm. in diameter. The distribution of them was rather interesting; they were situated almost directly beneath the pleura like small infarcts. The only other metastasis was one small nodule in the liver. In the left renal vein there was a free thrombus about 3 cm. long, quite firm, but section of it showed no tumor cells. The right ovarian vein was much dilated and contained a thrombus, in which also no tumor cells were found. The ovaries were practically normal; they were not enlarged or cystic, and contained a few early corpora fibrosa.

Microscopically the growth did not show the typical appearance of a chorio-epithelioma. The primary tumor was so necrotic that very little could be determined as to its structure, but in the uterine muscle about it were many multi-nuclear and mono-nuclear giant cells, probably of syncytial origin. In some fields these were apparently invading the uterine vessels. The smaller metastases consisted of dense fibrin resembling canalized fibrin of the placenta, and in the periphery of nodules were giant cells similar to those found in the uterus. The larger metastases differed only in containing masses of blood, due apparently to secondary hemorrhage into the nodule. Occasionally a few cells with clear, pale protoplasm and large vesicular nuclei were found, which resembled the cells of Langhans, but none were found which were absolutely characteristic. Following Marchand's classification, this tumor would fall under the atypical chorio-epitheliomata, and according to Dr. Ewing's classification would be called probably a syncytioma. It would seem that currettings from such a uterus would be rather difficult to distinguish from the conditions which he classifies as syncytial-endometritis, though the nuclei are larger and more pyknotic than would be found in such a condition and might enable one to make the diagnosis of malignancy. Judging from the clinical course, a secondary sepsis may have had much to do with the fatal outcome, though it seems hardly possible that a patient could recover after such extensive metastasis. The gross appearance seems to indicate clearly the malignant character of the tumor.

Discussion:

Dr. Larkin: I have not had an opportunity of looking at the sections, but I am struck by the short duration of the case, which resembles in this respect a similar one which I have seen in which the pregnancy occurred in June and death took place in September.

I wish to comment upon one point in Dr. Hopkins' presentation—that is, the occurrence of giant cells beneath the peritoneum of Douglas' cul-de-sac. This is of importance, especially in inflammatory conditions of the uterus not connected at all with tumor growth. It may be of very great importance in the diagnosis of a preceding pregnancy, since it has been found that the large wandering giant cells may migrate out through the uterine wall and be found underneath the peritoneum in the cul-de-sac.

Some time ago we saw a specimen from a case of abortion where the only evidence of that abortion was the finding of giant cells right underneath the peritoneum. In fact, in cases of abortion, after complete curettage of the uterus, I have noted the presence of large giant cells deep down in the musculature, far distant from any point which could be reached by a curette.

INTERNAL HYDROCEPHALUS, WITH SPECIMENS SHOWING OCCLUSION OF AQUEDUCT OF SYLVIUS AND OF FOURTH VENTRICLE.

M. G. SCHLAPP AND J. B. GERE.

We wish to present to you this evening four cases of internal hydrocephalus. I do not wish to dwell upon the general symtomatology of internal hydrocephalus, but lay particular stress upon the pathological findings in these four cases. In two of these cases I wish, however, to present some clinical data which, in connection with the pathological findings, make them of more interest.

The material of the first of these cases was sent to me by Dr. Ernest Sachs, whom I wish to thank for the same. This case was a male child three and a half years old who, the mother stated, was born with a large head, but up to nine months previous to its death seemed otherwise perfectly well. Nine months previous to the child's entrance to the hospital, he had a fall, after which he was unconscious and vomited repeatedly. One month after this fall the child became unconscious and developed a well-defined epileptic attack. Afterwards the child complained much of headaches and had several epileptic seizures. Five months after the injury, the child began to walk with an uncertain gait, and this became so marked that he could not walk or stand without falling. Vomiting increased, the child developed attacks of temper, became very irritable and excessively nervous. A spastic condition of the legs and arms, the Babinsky reflex and other symptoms typical of hydrocephalus were present. An exploratory operation was performed on April 5, 1911, and at nine o'clock on April 6 the child died. Specimens were sent to me cut through the crura, showing a complete occlusion of the aqueduct of Sylvius. We must infer that this closure of the aqueduct of Sylvius existed from the earliest period in the development of the child's brain and the fall which the child had can be considered as an injury which had a tendency to increase the cerebro-spinal fluid in the lateral ventricles, which in turn caused a marked increase of the symptoms.

No. 2.—Male child five and one-half months old, from the service of Dr. Howland, Bellevue Hospital. Pathological material was kindly given us by Dr. Charles Norris. Mother states that she noticed no abnormality about the child until the second month of his life. Then her attention was called to the fact that the child was developing a large head. Shortly after this time the child began to have peculiar spasms, lasting about five minutes, during which time the arms and legs became very stiff. When the child was four months old, it was taken to a hospital in the city where a lumbar puncture was made and about a pint of cerebro-spinal fluid removed, after which the child improved considerably. This improvement, however, did not last more than a week or so, when again the symptoms grew worse and the child was brought to the hospital, March 13, and died on March 27. There is no family history of any kind pointing to a possible etiological factor. The greatest circumference of head, 63 cm. Occipito-mental circumference, 61 cm. Occipito-frontal diameter, 22 cm. Occipito-mental diameter, 21 cm. Biparietal diameter, 17 cm. Bitemporal, 13½ cm. Sub-occipito-bregmatic, 18 cm. The specimens of this case show very clearly an occlusion of the aqueduct of Sylvius and one may see that this occlusion is brought about by a distinct proliferation of glia cells which have practically erased the contour of the central gray matter. There is a distinct increase of cells presenting the appearance of a glioma, and not only an increase of glia fibrils.

No. 3.—Female child two and a half years old, which was born with a large head and the extremities completely paralyzed. It has never been able to move them. She takes nourishment fairly well. On admission to the children's service at Bellevue Hospital, it was found that although there was complete paralysis of the extremities, the child, so far as could be determined, reacted to sensory irritations, particularly to the prick of a pin, by crying. The child was blind and did not seem to hear, but when the child cried or seemed to smile, the movements of the face were carried out with perfect co-ordination. This showed that co-ordinated movements of the facial muscles were possible through emotional stimulation. I show you here a photograph of the child's head with the head of a normal child beside it, and you see the very marked difference in size. At the autopsy it was found that this child had no cerebral cortex. The cerebellum was present, although quite small. The basilar ganglia were present, but were somewhat diminished in size. The cortex being only a thin membrane, is in some places translucent, in other places slightly thicker and showing microscopically a few irregularly shaped nerve cells. By these specimens you see that the pyramidal tracts were entirely missing on account of the absence of motor cortex. How can we account for the co-ordinate movements of the face, the central motor neurons being absent? It is a well-known fact that as we trace the phylogenetic development of the central nervous system from lower animals to higher animals, the function of motion is transferred from the basilar ganglia to the motor cortex. If, for instance, the motor cortex of a dog or cat be removed, it is found that these animals are still capable of walking, although in a disturbed manner, showing that a center other than the motor center in the cerebral cortex still has some influence over the movements of the extremities. This center, no doubt, is situated somewhere in the basilar ganglia. If the motor cortex of the human being or the higher monkeys is removed, we find that the extremities are totally paralyzed. Here the motor function has been completely transferred from the basilar to the motor cortex. It seems, however, that this transference of the motor function has as yet not taken place completely in movements of the face, and particularly has it not taken place in *emotional* movements of the face, so that we can say that the emotional movements of the face are still to a certain extent vested in the phylogenetic earlier motor centers of the basilar ganglia. This case having no motor cortex in the cerebrum distinctly proves this conclusion.

In this case you also see that the aqueduct of Sylvius is completely closed.

No. 4.—A female child, six months old. The parents were alive and healthy, two brothers, twelve and nine years of age, were living and well. Two sisters, both delivered instrumentally, died about an hour after birth. Whether their heads were larger than normal could not be ascertained. Otherwise, the family history was negative.

The child was normally born, without instruments. At the age of six weeks it had "bowel trouble," accompanied by "sick spells," during which it would remain unconscious for a whole day at a time. At the age of three months, the child had convulsions with twitchings of her entire body lasting about five minutes. The bowels were very constipated. The mother thought that the child's head had always been large, and had noticed that one eye had "turned out" since birth. It had never attempted to raise its head, nor did it appear to see. However she took her feedings well, and was well nourished.

Occipito-frontal circumference, 19½ in.; occipito-bregmatic circumference, 18¾ in.; fronto-mental, 19¾ in.; from the top of one mastoid to the other over the head, 15½ in. Anterior fontanelle open. The child had no teeth.

An operation was performed by Dr. John Hartwell, for the drainage of the ventricles of the brain into the peritoneal cavity. A description of the operation and a more detailed clinical report will be published elsewhere.*

At the autopsy there was found a very interesting condition, in that the whole fourth ventricle was completely obliterated by the proliferation of choroidal cells. We found, beginning at the lower end of the fourth ventricle, choroidal cells growing from a peduncle situated at the raphe of the medulla. As we ascend cephalically, these choroidal cells increase in quantity, and in the region of the sixth nucleus, they entirely fill the fourth ventricle. Here, as well as at other places, the choroidal cells invade the nerve tissue of the cerebellum and also of the medulla and pons, in typical neoplastic fashion. The aqueduct of Sylvius, throughout its course, is completely obliterated, not by choroidal cells, but by the proliferation of the surrounding glia cells. At some of the points where these choroidal cells have invaded the nerve tissue of the cerebellum and medulla, we find them arranging themselves in such a way as to form the walls of cysts and to take on the characteristic formation of ependyma cells. These choroidal cells are unquestionably spongioblastic cells derived from the same mother cells from which the glia as well as the ependyma cells develop.

A fuller description of these four cases will appear later.

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*We are indebted to Dr. John Hartwell for the specimen.

A COMPARATIVE STUDY OF METHODS FOR STAINING THE CAPSULES OF BACTERIA.*

GEORGE BAEHR AND JOHN KANTOR.

In accordance with the fact that the various methods suggested in the past have differed from each other primarily in their respective methods of fixation, we have chosen for this study procedures which appeared to be representative of the different methods.† After heat fixation, as exemplified by the welch[1] and Hiss[2] methods, shrinkage and distortion of the capsules were usually observed, and not infrequently capsules were not demonstrable although by other procedures they could easily be obtained. The results obtained with the Welch method were as a rule more satisfactory than those with the Hiss, and this we interpret as being due to the use of glacial acetic acid in the former. Drying of the smear previous to fixation usually had a very deleterious effect upon the preservation of the capsule, and this accounts in part for the relative inferiority of the Welch, Hiss, Wadsworth[3] and Medalia[4] procedures.

Many of the methods studied leave the albuminous menstruum, with which the smear is made, as a more or less deeply stained background. The best examples of these are the osmic vapor method of Weidenreich[5-6] and the tannic acid method of Rosenow.[7] Aside from the fact that this prevents a clear definition of the capsular outline, it frequently results in the production of artefacts such as retraction zones, the edges of which may be sharply stained. Such pseudo-capsules we have observed with B. coli. B. typhosus and other non-encapsulated bacilli. We know from Rosenow's[8] work that the entire capsular substance is stained by his method and therefore when the retraction zone is wide one can easily see that it is transparent and unstained and rule it out as an artefact. But when the retraction zone is exceedingly narrow, the stained margin of the albuminous background may envelope the organism very closely, simulating a capsule almost exactly.

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*Work done under the tenure of the Eugene Meyer, Jr., Fellowship in the Pathological Laboratory of the Mount Sinai Hospital.

†The following is a preliminary communication. More complete details of the work will later be published elsewhere.

If the procedure described by Buerger[9] is carried out correctly, the fixative (Zenker minus acetic acid) applied to the smear at the moment when the edges begin to dry and left on for not longer than three to five seconds, the background is completely eliminated and the organisms and their capsules are well fixed. The capsular outline, in the case of the pneomococcus, for example, is stained intensely and the capsular material much less deeply than the outline.

We believe that we can prove that this increased depth of staining of the capsular margin, as obtained with the Buerger method, is not dependent upon an appreciable amount of shrinkage. It appears to be due, more probably, to an increase of the normal concentration of protein or other substance at the periphery of the capsule. Not only is it not a disadvantage, but it is an important factor in accentuating the morphological differences between the capsules of pneumococcus, the streptococcus and streptococcus mucosus. Buerger[10] has described a pneumococcus type of capsule, a streptococcus type, and a mucoid type which includes the streptococcus mucosus and b. mucosus capsulatus. Several observers[3-11] have emphatically denied the existence of such distinctive types. From our observations we were enabled to ascertain that in every instance the capsule staining method employed was the cause of their disagreement, for by using these methods we also could not obtain any morphological differences. Even if these so-called types are artefacts, as has been claimed, the fact that they are differential would warrant the use of any method which would demonstrate such differences. But that they are not artefacts is easily proven by examining the organisms unfixed and unstained, which is easily accomplished by a hanging drop made by using a one per cent. collargol suspension.

Besides preserving the type capsule, a good method must bring out the poorly developed capsules. With many of the procedures, for example the Welch, Hiss and Wadsworth, we frequently could not demonstrate these degenerate forms. The Buerger and Rosenow methods proved most satisfactory in this regard. The Rosenow, the osmic vapor and the other methods in which a uniform background is retained, on many occasions produced pictures with non-encapsulated organisms which were very confusing. On the other hand it has been our experience during this study that the Buerger method when executed properly never failed to show a capsule when one could be demonstrated by any other method, never produced anything around a non-encapsulated bacterium which could be easily mistaken for a capsule, and most uniformly and distinctly demonstrated the various types.

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[11] Hiss, Jr., P. H.: *J. Exp. Med.*, 1905, VII, p. 547.

Discussion:

Dr. Buerger: Dr. Baehr has covered this subject so thoroughly that I can add very little, my experience in capsule staining dating back six or seven years. However, there are a few things I might point out. There can be no question about the fact that the capsules, as they appear with the Zenker method, are not retraction zones. When, in a mixed culture, the field is absolutely clear and there are many other bacteria without capsules, we have sufficient ground for believing the capsules to be true ones and we need not dwell further on the detailed arguments. I think Dr. Baehr's point as to the value of a clear background is very well taken. The reason for the failure by so many men to detect encapsulated organisms, is due to diffuse staining, and the absence of a clear field. In my experiments with the various fixatives, including osmic acid, Fleming's solution, and formalin, I came to the conclusion that Zenker was the best for the particular purpose in question.

The capsule of the pneumococcus is stained as a rule faintly or not at all. By stain, of course, I mean a complete readily recognizable staining of capsules, something that everyone would at once recognize as a tinctorial effect.

Dr. Libman: The question of the existence of a type pneumococcus capsule is not purely of academic interest, but is of diagnostic import. It is, in general, important for us to know as soon as possible exactly which organism is causing the infection. This is particularly true since the introduction of vaccine and serum therapy. In actual practice there are two conditions in which it is very valuable to know as soon as possible whether an invading organism is a pneumococcus or not. These two conditions are sinus thrombosis and pneumococcus peritonitis. In our experience we have not found any cases of sinus thrombosis due to the pneumococcus. If, therefore, in a case of otitic disease a pneumococcus is found in the blood culture, we would not be ready to diagnose infection of the sinus, and would therefore not make the same indication as we would were a streptococcus present.

There exist occasionally cases of so-called idiopathic streptococcus peritionitis. The cases of idiopathic pneumococcus peritonitis are much more frequent. When a surgeon is operating upon a case of peritonitis and cannot find a focus of entry, he can close the abdomen with much greater assurance if we report a pneumococcus in the exudate (even if he has not looked for the primary focus).

EXPERIMENTAL POLIOMYELITIS, PRODUCED IN MONKEYS FROM THE DUST OF THE SICKROOM.*

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Struempell, in 1884, and Pierre Marie, in 1885, were the first to call attention to the infectious character of poliomyelitis or the Heine-Medin disease, as they called it. As civilization became more and more complex, and population more dense, the disease became more widespread and its epidemics assumed larger proportions; so that Wickmann, Harbitz, and Scheel, in 1903, were the first who made a thorough study of the epidemics in Sweden and Norway, confirming the infectious character of the disease.

Landsteiner and Popper, however, proved this by the epoch making inoculations of the emulsion of the brain and spinal cords of infected children, who had died from this disease, into monkeys, intraperitoneally, reproducing the exact type in these animals. Levaditi and Landsteiner then showed that the virus is filterable through a Berkfeld filter, a discovery without which our work would have been an impossibility.

Flexner and Lewis, Strauss and Huntoon on this continent, and Romer, Leiner and Wiesner, Krause and Meinecke abroad, in 1910 confirmed these experiments. Flexner and Lewis in addition found that the virus was excreted through the mucous membrane, and were able to transfer it from monkey to monkey, but the mode of infection, the source, and the manner of dissemination of this disease were still mysteries, so that we were not certain what preventive measures to adopt for its eradication.

On February 10, 1910, before the State Medical Society, Dr. Flexner said: "Up to recently we have had no satisfactory

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knowledge of the causation of this very destructive disease. Indeed, our ignorance has been so profound that we had no knowledge as to how the poison gained access to the body, and we have, therefore, been unable and are still unable to carry out any efficient prophylaxis against the disease. In other words, the medical profession has been quite as helpless in respect to this disease as has been the laity." In September, 1910, he published an article in which he maintained that the nasopharynx might be the portal of entry, and, in an article published in August, 1911, he made the following statement: "Insect contamination with the virus would serve, were it proved not only to be an experimental possibility, but to occur in nature, to clear away any present apparent discrepancies in the epidemiology of the disease. In this connection it should be stated that not only does epidemic poliomyelitis spread over a wide territory, but its spread is not promiscuous, but along the routes of human travel. Therefore, insects that seek human habitations and routes of travel, that possess the power to migrate over a considerable territory, that affect all classes of society, that abound during the period of greatest prevalence of the disease, and that do not wholly disappear at any season, should be the first to come under suspicion."

Dr. J. M. Armstrong (*Pædiatrics*, August, 1910) makes two significantly inconsistent statements: "During the epidemic in St. Paul, Minn., seventeen cases occurred, infected from one another by visiting relatives." And yet he continues in another paragraph: "After investigating the hypothesis"—not mentioning how—"that the cause of this disease was due to food infection, water, dust, presence of domestic animals and insects, etc., these theories were abandoned as inadequate, and we came to the conclusion that the causative agent was a facultative parasite which might lead a saprophytic, saprozoic existence in the body and that conditions of fatigue or unknown phenomena cause it to change from a feebly virulent agent to one of extreme toxicity."

Robert W. Lovett (*Pædiatrics*, August, 1910, pp. 574, 575) summarizes a report of 150 investigated cases of poliomyelitis which occurred in 142 families and concludes: "The evidence of communicability in our series of cases is a very important matter. We had instances of direct contagion from child to child, with an incubation period of one to fourteen days. We had a number of instances of what appeared to be indirect contagion by a healthy carrier, and finally we had eleven instances in the 150 cases where the disease followed intimate contact with persons with old infantile paralysis, often of many years' standing. Instances of what would appear to have been contagion occurred in thirty-five out of the 150 cases. Of the 150 patients, sixty-two were swimming or wading in stagnant water just before the onset." . . .

Paul Krause (*Deutsche medizinische Wochenschrift*, October 21, 1909) and others report cases, where several members of the same family were in several instances simultaneously affected. He concludes that the infection is through the alimentary canal and therefore through articles of diet.

F. Mueller (*Münchener medizinische Wochenschrift*, 1909) states that in the epidemic of Hesse-Nassau the disease showed a predilection for certain villages, streets, and groups of houses. There was no evidence that the infection was conveyed through food or vermin, but it was apparently transmitted from person to person.

These are the opinions held by those who ventured to give any. We have been unable to find any theory that would coincide with ours.

The theory, which we are now in position to prove, was based on the following facts:

1. The disease is eminently an infantile one, occurring in dry season.

2. The character of the neighborhood and of the living premises, where it occurs, plays no material part in the spread of the disease. In other words, it can occur anywhere.

3. Several children in the same family may be attacked successively. In a given house, children are attacked in differ-

ent families in fairly quick succession, and along lines of neighborly communication.

From these facts we have concluded that the virus lurks in the dust, and that it must be contagious.

In the early part of 1910 we began to collect sweepings of the rooms where cases of poliomyelitis occurred and to prepare them for injection into monkeys. Throughout our experiments we have used (*Macacus rhesus*) monkeys and for purposes of accuracy we shall speak of our experiments with monkeys Nos. 1, 2, 3, 4, 5, and 6.

In March, 1910, we collected sweepings from nineteen cases of poliomyelitis of from six to three months' standing after the onset of the paralysis. These sweepings were collected from rooms where the children were playing and sleeping, by cleaning the floor and the wooden trimmings around the walls, and were dried for days, then sifted and macerated in normal salt solution for a week, then filtered through paper and a Berkfeld filter. This filtrate was kept on ice for six days. On April 8, 1910, we injected monkey No. 1 under the dura through a trephine opening in the right frontal skull. On April 15, seven days later, the animal became quite sick, but completely recovered after three days. The spinal fluid which was withdrawn before injection was not examined and no spinal fluid was withdrawn at the time of illness. A few days later we prepared extracts in the crude manner described from nasal discharges of some of those patients from whom the sweepings were obtained and injected them intraspinally into monkey No. 1, but without noticeable result.

Toward the end of April we obtained through the courtesy of Dr. Strunsky a sample of sweepings from a case of six weeks' standing. This was also handled in the manner described, and on May 2, 1910, we injected monkey No. 2. We thought monkey No. 1 might be immune and were anxious to take every precaution possible not to confound negative results with positive failures. On May 6, four days after the injection, the monkey became very ill and both monkeys Nos. 1 and 2 were killed and autopsies were performed. Macroscopically, monkey No. 1 was normal, but monkey No. 2 presented a hyperæmia of the vessels throughout the brain and spinal cord. Dr. Dunlap was kind enough to examine these cords and following is his report: "In monkey No. 2, in the neighborhood of several vessels of the pia, especially the veins of the posterior portion of the cord, there were collections of small dark staining nuclei of lymphoid cells, these undoubtedly indicate some sort of reaction, possibly an infection (?), but I was unable to discover anything to account for it. In the gray matter I found very little that I could recognize as pathological. In the specimen of the lower cervical region, as you will see, there are scattered extravasations in the gray matter, especially on one side; but this was the only level at which I found such changes. I thought the number of stellate cells might be slightly increased in both animals. Neuroglia increase is certainly slight, if present at all; I was not able to satisfy myself that there was any reaction.

"I do not know the conditions of your experiment, but I understood that the work was undertaken with a view to producing experimental poliomyelitis; if such is the case the cords in neither of these animals show any changes which I should consider in any way characteristic of that process, as it occurs in human spinal cords, the changes of monkey No. 1 being confined essentially to the meninges, more especially in the neighborhood of the blood vessels."

This report convinced us that we were following a faulty technique and in May, 1911, we began our experiments again.

May 16, 1911, we injected into monkey No. 3 an extract of sweepings from three different cases which occurred in one house. These were macerated with normal salt solution for a few days and filtered through a Berkfeld filter. The cases were of two days' and two weeks' standing, respectively. The spinal fluid was withdrawn prior to injecting into the animal and examined. The monkey was then etherized and trephined in the right frontal skull and injected through the brain into the ventricle with four cubic centimetres of the prepared filtrate. This filtrate, as well as those injected into monkeys 1 and 2, were inoculated into ascitic broth media and subsequently proved sterile after a period of several days' incubation. Wtihin twenty-four hours after the injection, the monkey rallied nicely and remained well until May 23, when it fell quite ill. It kept to a corner in its cage, lying down most of the time. May 24, the spinal fluid was withdrawn and examined. On this day it was constantly lying flat on its abdomen and upon examination we found the patellar and plantar reflexes gone in the right hind limb. May 25, there was a partial paralysis of both hind limbs and on the day following all four extremities were paralyzed. There was also a rigidity of the muscles of the neck, and when placed on the dorsum, the animal could not turn. Pupils were normal and reacted well; there was no strabismus. The reflexes in the hind limbs were absent and on extending the limbs the animal winced, evidently from pain. The animal was killed, but the autopsy failed to show any meningitis or encephalitis. A blood clot 1 mm. by 3 mm. was present in the fourth ventricle. This time the spinal fluid had a lymphocytosis and a positive globulin reaction. Macroscopical and microscopical findings of monkey No. 3 were negative. We have, however, made an emulsion of its brain, cord, and ganglia for testing on the other monkey.

May 26, monkey No. 4 was injected intracerebrally with the emulsion of monkey No. 3, after first withdrawing the spinal fluid, and up to August 19 showed no reaction. On this day this same animal was again injected intracerebrally with an extract of sweepings of a case of one week standing which we received through the courtesy of Dr. Sayre on August 12. The extract was then prepared in the following manner: The sweepings were shaken constantly for six hours with 100 c.c. of normal salt solution and then strained through cotton; 30 c.c. of this filtrate were filtered through a Berkfeld filter and evaporated in a vacuum in the course of three days to 25 c.c. A pure culture of *Bacillus prodigiosus* was added to the extract prior to filtering it through the Berkfeld, in order to test the permeability of the filter. A subsequent inoculation of this filtrate into blood agar proved it to be sterile. The possibility that *Bacillus prodigiosus* toxine may have had any effect upon the results is excluded by the fact that subsequently from monkey No. 5 the virus was transferred to monkeys Nos. 4 and 6 by the injection of an emulsion which was not passed through a filter.

The procedure was the following: Monkey No. 4 was tapped in the lumbar region and 4 c.c. of a clear fluid were obtained and examined for lymphocytes and globulin reaction. The globulin reaction, according to the Noguchi method, was negative. The monkey was etherized, and through a trephine opening in left frontal skull, 5 c.c. of prepared extract were injected through the brain substance into the left ventricle. Half an hour after the injection, the animal was up and about, and quite lively, and continued in an apparently good state of health up to August 26, seven days after the injection, when it became nervous, trembling at the least disturbance, dull, and listless and kept to a corner of the cage. On the following day, we noticed a flaccid paralysis of his right forepaw, a characteristic wrist drop, and a disappearance of the symptoms of malaise. His condition ever since remained normal with the exception of the paralysis. We did not kill this monkey, because the paralysis was rather insignificant, and we were doubtful of the results. August 30, a lumbar puncture was made, and one c.c. of a clear, spinal fluid was obtained and examined.

August 29, we obtained, through the courtesy of Dr. Wallrath, of Staten Island, the sweepings of a room wherein a four-year-old child was stricken with poliomyelitis, and had been then two days paralyzed. In this room the child passed most of its time, and was confined to bed.

The negative results in the first three monkeys, and the doubtful one in the last experiment on monkey No. 4 suggested that our technique was at fault, and we resolved to use sterile water instead of normal salt solution, and obtain the filtrate ready for injection at the earliest possible moment after the collection of the sweepings.

Accordingly, this new installment of dust, about fifty grammes, was macerated over night with 30 c.c. of sterile water, and then shaken for one hour. The mixture was filtered through a paper filter, and 15 c.c. of this filtrate were passed through a special Bougé filter, under high pressure, within an hour.

Cultures of this filtrate were made on bouillon and blood agar. The cultures grew a Gram positive coccus within twenty-four hours, probably a subsequent contamination, for none was found in the animal after the autopsy.

Within eighteen hours after the collection of this dust, 5 c.c. of the filtrate were injected into monkey No. 5 through the spinal fluid, and 8 c.c. were injected subcutaneously.

After the injection the animal was depressed and sullen, and inattentive to its surroundings. On the following day the monkey was perfectly well and remained so until September 4, six days after the injection, when it was reported very ill and paralyzed. September 5, the animal presented a flaccid paralysis in the right foreleg, and a marked paresis of both hindlegs, most pronounced in the left. He was able only with great difficulty to move about in his cage. A lumbar puncture was made, but only two drops of a gelatinous material were obtained from the needle, after withdrawing it from the canal.

September 6, he still showed all symptoms mentioned, but in a more marked degree. A spinal puncture was again made, and two drops of a gelatinous material were obtained.

The animal was then killed and following are the results of the autopsy: There was a marked hyperæmia of the meninges in the lumbar region, and a lesser one in the cervical region; the vessels of the brain, cortex, and cord were markedly congested. This hyperæmia was evident at all the levels of the cord, in the medulla, in the pons, the ventricles, and basal ganglia. The cord and brain presented an œdematous condition. On section, one could note hæmorrhages into the gray substance of the cord, especially in the lumbar and cervical regions. There were also some hæmorrhagic foci in the medulla, while the white and gray substance of the brain presented, macroscopically, a normal appearance. The vessels in the ventricles were very much congested. The viscera presented the following changes: Areas of congestion in the middle and lower part of the upper and the lower lobes of the left lung. The spleen was firm and congested, but not enlarged; all the visceral vessels were very much injected. All other organs and glands were, to all appearance, normal.

Sections of the spinal cord, cerebellum, pons, medulla, brain, spinal and basal ganglia were now emulsified in 50 c.c. of normal salt solution and preserved for injections. We wanted first to await the histological findings before injecting another animal. For diagnostic purposes a few sections were hastily hardened and stained.

The sections presented the following pathological changes (the lumbar and cervical sections alone being examined under the microscope):

There was a diffuse infiltration of round cells into the pia and gray substance of the cord, both in the anterior and posterior horns, but more so in the anterior. From accompanying photomicrographs it can be seen that the inflammation was greatest in the anterior part of the cord, following the pial processes into the depth of the anterior fissure and along the sheaths of the central vessels. The congestion in the gray matter was quite extensive, as evident by the engorgement of the capillaries. We further noted a circumvascular and interstitial round cell infiltration of two types of round cells, characteristic of poliomyelitis, also endothelial and polymorphonuclear cells. The ganglion cells began to show degenerative changes. There was also a marked gliosis, an additional evidence of the disease. We call attention to some features in order to leave the least possible doubt as to our success. Cultures made from the brain and cord of monkey No. 5 on the date it was killed proved negative. The autopsy revealed no *purulent* meningitis, but rather a hyperæmia of the lumbar, and cervical meninges. In examining the fluid drawn from the spinal canal on the day before the animal was killed, and on the day of making the autopsy, no bacteria were seen.

Our diagnosis having been confirmed on September 8, we

TABULATED RESULT OF THE EXAMINATION OF THE SPINAL FLUIDS OF MONKEYS NOS. 3, 4, 5, AND 6

	Date.	Amount.	Clearness.	Color.	Coagulum.	Sediment.	R. B. C.	W. B. C.	Ratio.	No. in one cubic millimeter.	Mon'n nuclears.	Small mon'nuclears.	Large mon'nuclears.	[illegible]	[illegible]	Bacteria	[illegible]
Monkey No. 3,	1911																
before injection	May 16	gtt. x	Clear	None	None	None	....	..	....	3	.	..	..	..	..	0	0
Monkey No. 3,																	
paralyzed	May 24	1 c.c.	Clear	Blood tinged	None	Slight amount	45	23	. .	230	2	96			1	0	0
Monkey No. 4,																	
before injection	April 27	4 c.c.	Clear	None	None	None	....	..	....	0	..	2				.	.
Monkey No. 4,																	
paralyzed	August 30	4 c.c.	Blood tinged	Yellow	None	Reddish	374	2	1:185	46	4	17	5	.	4	0	
Monkey No. 5,																	
before injection	August 31	5 c.c.	Clear	None	None	None	47^1	9	1:5.2	44^2	10	46	5	0	0	0	..
Monkey No. 5,																	
paralyzed	September 5	gtt. ii	Blood tinged	Red	Gelatinous	None	Many^1	..	....	..	48^1	10	6	4	0	0	..
Monkey No. 5,																	
paralyzed	September 6	gtt. ii	Cloudy	Red	Gelatinous	None	Many^1	..	....	..	46	18	28	8	0	0	0
Monkey No. 6,																	
before injection	September 8	3 c.c.	Clear	None	None	None	2	4	1:2	4	..	32	1	0	0	0	..
Monkey No. 6,																	
paralyzed	September 22	gtt. ii	Blood tinged	Bloody	......	.....	430	0	....	..	6	4	8	..	..	0	0

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[1] Blood present in fluid.

[2] Gay and Lucas, article in *Internal Medicine*, vi, 330-338, 1910.

injected monkeys No. 4 and No. 6, each with 6 c.c. of the preserved emulsion, intraspinally, and 8 c.c. subcutaneously.

Monkey No. 4, which we concluded might have had a poliomyelitis, immediately after the injection was thrown into a violent trèmor and became quite ill. He could hardly be aroused and remained motionless for the rest of the day. The next morning he completely recoveerd. This was probably an instance of anaphylaxis due to the previous cord emulsion. On September 14, six days after the injection, this monkey became very ill and on the following day the right fore limbs and hind limbs became paralyzed. On September 16, eight days after the injection with emulsion of monkey No. 5, all four extremities were involved. The paralysis was of the flaccid type. Soon the muscles of the back and neck became affected so that the animal was unable to move even its head, and had to be fed. The reflexes were all gone and there was no response to the faradaic current in any of the extremities. Monkey No. 4 then reacted positively and thus proved that monkey No. 5 had poliomyelitis. It died on September 21 and the autopsy was made the same day.

Monkey No. 6, which was also injected with an emulsion of monkey No. 5, was quite ill on September 15, seven days after, but seemed to have been able to move about freely. It remained in this condition till September 22, fourteen days after the injection, when suddenly a flaccid paraplegia developed, and on the following day a complete paralysis of all four extremities. The monkey was then killed and an autopsy was performed.

Thus we had infected two monkeys from monkey No. 5.

In order to make the work more comprehensive, we may propose the schematic table found on this page.

The autopsy findings of monkeys Nos. 4 and 6 were as follows: No meningitis of either brain or spinal cord; the œdema of the entire cerebrospinal axis was very marked; the vessels were very much injected; on section there were punctate hæmorrhages at all the levels of the cord, medulla, and pons. In monkey No. 6 there were some adhesions of the spinal dura at the lumbar and cervical levels. The visceral vessels were congested, but the viscera were all normal in appearance.

Microscopically, as seen in the photomicrographs, the sections present the same characteristics as those of monkey No. 5, with the exception that they are rather more intense, especially so in the lumbar region of monkey No. 6.

Cultures made from the ventricles and subdural spaces of brain and cord on ascitic broth and blood agar media, proved negative and no bacteria were seen on sections.

We have thus proved our theory that:

1. Poliomyelitis is propagated by dust, and we may also conclude that

2. the nasopharynx probably is the point of entry.

3. Acute poliomyelitis is both infectious and contagious.

It becomes perfectly evident that prophylactic measures should be most rigidly carried out in order to check the spread of this disease.

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DEMONSTRATION OF SPECIMENS.

DR. J. H. LARKIN.

(*a*) *Melano-Sarcoma.*—The first case is a case of Melano-Sarcoma of the Liver, taken from an individual about 64 years of age, who had his eye removed about one and a half years ago at the New York Eye and Ear Infirmary. After the removal of his eye, he commenced to undergo progressive emaciation with enlargement of the abdomen. Finally he was taken to Bellevue, where he remained for some time, the diagnosis there being Cirrhosis of Liver. After remaining perhaps a week or more, he was sent over to the Island; there he remained about three weeks. The history having been gone over and the absence of his eye having been inquired into, we obtained possession of the eye, which was removed one and a half years previously, and, on examining it, found a melano-sarcoma of the choroid. He died four days thereafter, the status at that time being as follows: There was marked cachexia, marked distention of the abdomen and pigmentation of the skin. No metastases were present in the bones or subcutaneous tissues.

At autopsy the particular feature of interest was the condition of the liver, which weighed 22¼ pounds. I present this specimen to-night as a very beautiful specimen of a Melano-Sarcoma; it shows a peculiarly interesting feature, that is, the transition in the type of the nodular or metastatic masses in the liver, which exhibit every gradation in size and in color, from a pearl white to a dense black. The only metastatic nodules in this case were found in the spleen, one medium sized nodule and several small ones. The urine obtained during life gave a pronounced melanin reaction, although this is now held to be of questionable clinical significance.

(*b*) *Acute Endocarditis due to an intermediate Diplococcus.*—The next specimen I have to show is one of some interest, and I must ask the indulgence of the Society for showing what at first sight may be considered a simple case of malignant endocarditis.

The specimens were taken from a young girl who was admitted to the City Hospital on August 29 and died September 28. She was about thirteen years of age, but she looked as if she was about eight years old. The history of this child briefly is as follows: Patient had scarlet fever about eighteen months ago, preceded by otitis, which had lasted for five or six years. Ten days before admission she began to complain of headache and chills. The physician called in detected a heart murmur, and as she had a temperature of 103°-104°, sent her to the Harlem Hospital, from which she was transferred to the City Hospital. She remained under observation until September 5, when her temperature ranged around 104°-105°, and at that time she had a very marked discharge from the ear, with some pain over the mastoid. She was operated on for a mastoid suppuration, and no great amount of pus was found. Her temperature ranged around 103°-104° and still kept going up. Four negative blood cultures were obtained; five days before death, however, there was obtained from the blood a diplococcus intermediate in type between streptococci and pneumococci. This organism, so far as it has been studied, corresponds morphologically and culturally with the diplococcus described by Rosenau, Libman and Celler in cases of endocarditis running a sub-acute course. If I remember rightly, in all the cases associated with this type of organism there have been old valvular or endocarditic lesions; this is apparently the first case which has occurred in a heart previously normal. The organism is not pathogenic for the laboratory animals, does not have any tendency to arrange itself in chains, and produces precipitation in serum-glucose agar. It is a non-capsulated diplococcus.

Petechial spots were found in the spleen, kidney and mucous membranes, but there was nowhere any abscess formed, and only one small infarct in the kidney. This seems to me of importance in differentiating a case of this sort from an ordinary streptococcus infection. In addition to the vegetations on the aortic valve, a number of anomalies were found. There were only two aortic cusps; the uterus was of the marsupial type with complete absence of the Fallopian tube on the right side. The ovaries on both sides were normal. There was oedema of the left lower extremity, due to a white thrombus of the left iliac vein.

Discussion:

Dr. Libman: I do not want to go into details just at the present time concerning the organisms found in these cases. When our paper was published, we left the question open as to whether the organisms usually found were changed pneumococci or changed streptococci. In previous studies made in the laboratory, we had often found that pneumococci change partially or almost completely into streptococci, but had never found the reverse to be true. From our experience, therefore, it would have been more natural to surmise that these organisms were altered pneumococci. Dr. Celler and I were, however, never successful in obtaining capsules in these organisms and, furthermore, cultures of these organisms were not dissolved by bile, as pneumococci are.

In our paper we stated that we could surely regard these organisms as altered pneumococci if we found any pneumococci which on cultivation from the body could be dissolved in bile, but which on later cultivation from the body were found insoluble in bile.

When we read Dr. Rosenow's paper, we obtained the impression that he found capsules on these organisms in the primary cultures from the body, and these capsules being of the type described by Buerger as pathogonomonic with the pneumococcus. We have obtained a type capsule hitherto on only one organism on direct cultivation from the body. As we have believed in the pathognomonic value of the type capsule, we must regard this particular organism as being a changed pneumococcus. Because of the apparent discrepancy of our results and those of Dr. Rosenow, I suggested to Dr. Baehr to make a comparative study of the various methods of staining capsules, in order to determine whether or not we were missing capsules on these cocci, due to the fact that we were using a method which would not give results as often as other methods might. As he will state to you in his report, he found that the method that we used gives capsules more regularity and better than any of the methods which he tried. Meanwhile, in a personal conversation with Dr. Rosenow, I learned that he obtained capsules only after repeated inoculations into rabbits, and then only with some of the organisms. He did not at any time obtain a capsule from a freshly isolated organism.

It is to be noted here that cases of endocarditis showing similar cardiac lesions to those shown by Dr. Larkin to-night, and the same clinical picture may be caused by the influenza bacillus. In the last few years certain evidence has accumulated which goes to show that the lesions in patients suffering from chronic infective endocarditis (or subacute bacterial endocarditis, as I prefer to call it) may undergo healing in part or entirely. In a study of our cases we have noticed a marked tendency to healing in some cases and, in a few, complete healing. Complete healing of the lesions, however, does not always go hand in hand with clinical recovery. The kidney lesions of this disease, as pointed out by Loehlein, appear to be quite characteristic. They are at present being studied in our laboratory and will be reported upon by Dr. Baehr.

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DR. W. G. MACCALLUM, *President*.

THE ISLANDS OF LANGERHANS AFTER LIGATION OF THE PANCREATIC DUCTS.

MARY BUTLER KIRKBRIDE, M.D.

The question of the persistence of the islands of Langerhans after ligation of the pancreatic ducts is of special importance when regarded from the standpoint of the relation of the islands to glycosuria. While it has been shown that glycosuria invariably occurs after complete removal of the pancreas, it has generally been accepted that ligation of the pancreatic ducts is not followed by glycosuria.

In 1909. MacCallum described an experiment in which one-third of the pancreas of a dog was separted from the main mass and the ducts ligated. Seven months later when this isolated portion was reduced to a mere thickening of the mesentery, the normal remainder of the gland was removed. Glycosuria followed but was slight, and lasted only three days, after which time a very considerable tolerance for sugar was attained. When, twenty-one days later, the pancreatic remnant was removed, extreme glycosuria resulted. Microscopically, this remnant showed masses of cells which, though morphologically like islet cells, were not so typical as to eliminate all doubt in this respect.

The present study was undertaken for the purpose of ascertaining by means of differential stains whether these groups of cells described by MacCallum and others were made up solely of persisting islet tissue By means of Lane's method the desired contrast in the staining reaction between the acinar and the islet cells was obtained. The pancreas taken from a normal guinea pig showed the islet cells filled exclusively with fine dark blue granules, while the zymogen granules of the acinar cells stained a reddish brown. The isolated pancreatic portion of a guinea pig, which had been operated on three weeks before, showed an increase of connective tissue, and the acinar cells greatly shrunken, while the islands of Langerhans appeared normal and their cells filled with blue granules. A third guinea pig was operated on in the same way and kept for nearly fifteen months. Microscopic examination of the fatty mass, which had replaced the isolated portion of the pancreas, showed no trace of acinar cells. But embedded in it were found small groups of cells whose cytoplasm was filled with typical blue granules. There could be no doubt that these cells belonged to persisting and actively functioning islands of Langerhans.

Several points are suggested by this preliminary study. First, that the contrast in the staining reaction between the granules of the acinar and the islet cells, as shown by Lane, can be confirmed. Secondly, that during the atrophy of the acinar cells and even long after the last traces of them have disappeared, the islet cells remained morphologically unaffected and filled with the granules which are peculiar to them. Taken together with the experiments of Dr. MacCallum, this seems to offer strong evidence in support of the view that the islands of Langerhans are especially, if not exclusively, concerned with the maintenance of the normal carbohydrate metabolism.

Discussion.

DR. EWING: I would like to ask if in the course of changes observed in these tissues, there was any evidence encountered of transformation of ordinary acinar cells into the type of islet cells?

MISS KIRKBRIDE: In some sections, I have occasionally found places where it is very difficult to say positively whether one has, or has not, to do with transitional forms. But, on the whole, I am inclined to think there are no transitions between the acinar and the islet cells.

CARCINOMA OF THE STOMACH WITH CURIOUS METASTASES IN THE LUNGS.

W. G. MAC CALLUM, M.D.

The peculiar lesions which appeared in the lungs in this case seemed to justify its being reported. The specimens were taken from a man aged 55 years who died with obscure symptoms of the growth of a malignant tumor in his lung. Nevertheless at autopsy the appearances were, at first sight, those of tuberculous infection of the lung. There were areas of consolidation scattered about through both lungs which on section had almost exactly the appearance of a pneumonic consolidation while the remaining lung tissue was studded here and there with small tubercle-like masses. There were, however, small lenticular thickenings of the pleura which suggested rather a tumor growth.

Examination of the abdominal viscera revealed a tumor of the stomach which occupied a large portion of the pyloric end of the stomach. It produced a diffuse thickening of the wall, but there was practically no ulceration and no marked contraction. The glands in the neighborhood of the pylorus and the head of the pancreas were involved, and the pancreas itself was somewhat invaded. The discovery of these lesions made fairly certain the diagnosis of secondary cancerous involvement of the lung.

The point of especial interest is the microscopical character of the growth in the lungs. The tumor, which had grown largely in the lymphatic channels, the walls of the arteries and veins, frequently leaves them and enters the alveoli, and in the areas which appeared to be consolidated, every alveolus is snugly filled with a mass of tumor cells. In none of these alveolar masses of cells could any blood vessels be found, and it seems as though the cells were growing there, bathed in the fluid which fills most of the alveoli and produces the condition of oedema throughout a large part of the lung. In this respect their growth resembles very closely that which one sees in the cultures of carcinoma cells made in a hanging drop of plasma on a slide.

The epithelial cells hang together very closely, as has been pointed out by Drs. Lambert and Hanes, in these cultures when the tissue employed is from a carcinoma; and are in sharp contrast in this respect with the cells of a sarcoma which tend to separate from one another and grow out independently. So, too, in the alveoli of the lung, the epithelial cells grow in solid masses with fairly smooth outlines, and one can hardly escape the impression that they find there a suitable nutritive medium and mechanical support and in which they grow practically as they would in vitro.

Discussion.

Dr. Norris: You see occasionally the microscopic picture which Dr. MacCallum has shown in the slides, when there occurs an aspiration of cells. Thus, when rupture occurs of softened epitheliomatous lymph-nodes into a bronchus, aspiration into the lobules takes place, and produces a similar appearance.

A CASE OF OVARIAN PREGNANCY.

I. C. RUBIN, M.D.

The patient from whom I removed this specimen was 24 years old, had been married three years, had one child two years of age. Previous and family history are of no interest in this case. Last menstrual period seven weeks before admission to hospital, which was a year ago last July. Patient was admitted to Beth Israel Hospital, in the service of Dr. S. W. Bandler. Two months before admission to hospital, she had rather sharp pain in the abdomen, localized especially in the lower half and more intense on the right side than on the left. At that time she noted a yellowish vaginal discharge; she had pains once or twice daily during the two months previous to admission; she also reported feeling chilly and feverish at times. Two days before admission there was vaginal bleeding. At the time of admission we noticed no bleeding of any kind, either at the vulva or escaping from the external os. Examination vaginally, elicited tenderness on the left side over a mass which seemed to be twice as large as an average normal ovary, but did not have the characteristic hardness. The ovary on the right side was also enlarged and tender.

The diagnosis made, in view of the irregular history, was ectopic gestation on the left side, also possibly associated with inflammatory disease. Gonococci were not found in either the vaginal or urethral smears.

On opening the abdomen, my attention was directed to a small amount (about 2 ounces) of yellowish fluid which was bloody, and which seemed to fill the posterior cul-de-sac. The uterus was in good position, though somewhat enlarged. The left adnexa were enlarged. The tube was bent backward. The ovary was attached to the posterior aspect of the broad ligament close to the uterus. On trying to deliver the ovary, I noticed that in the area of attachment to the posterior ligament there was a rather irregular, chocolate-brown mass which protruded from the ovary, and which looked very much like a degenerated corpus luteum. At the same time, in the manipulation, I brought to view a small plum colored mass, about the size of a hazel nut. I was not certain at the time whether it was a corpus luteum or a bloody mole. The uterine serosa seemed oedematous and tore through when grasped with tenaculum or forceps.

The tube was removed at its uterine insertion. The right adnexa showed cystic degeneration of the ovary. The tubes on either side were practically normal. One point of interest was that the left tube was rather short. I did not notice whether it was short in comparison to the right, but after straightening it out, I saw it was a short tube.

Patient made an uneventful recovery. I curretted her without anaesthesia, after waiting two weeks for the possible discharge of a decidual cast, and examined the currettings as well to make the study of the case complete. The specimens that I examined were the left adnexa, a small portion of the ovary of the right side and the uterine currettings. Under the microscope one of these sections showed a blood clot surrounded practically on all sides by an ovarian cortex. The first section taken through the apparent level of the rupture showed very few chorionic villi; these were in a very poor state of preservation. There was not the typical double layer of epithelium but the myxomatous stroma was so characteristic that there was no question about it. Another section showed groups of these chorionic villi, unquestionable in character, which were immediately underlying the ovarian cortex. The cortex itself showed a comparatively normal structure. There were typical ovarian elements, *i. e.*, follicles in all stages of development, from the earlier form to the mature follicle. On the surface of one portion of the ovary were several groups, spherical and ovoid, which showed characteristic decidual cells. These were separated by a cleft which was lined by flat cells that resembled endothelial cells but on comparison with some of the residual germinal epithelium, I am inclined to think they are true epithelial cells. There was no remnant of the corpus luteum except for a number of pigmented cells at the circumference of the blood coagulum, some of which suggested very strongly typical luteal cells. The tube on the same side, several sections being made, showed no decidual reaction whatever. The ovary of the other side—the small piece that was examined—showed a rather peculiar condition of what might be called a theca-lutein cyst. I mention that to submit it for your consideration, as I am not quite certain about its significance. The uterine currettings showed nothing striking. I was surprised not to find any evidence of decidual reaction.

Another point which is of some interest in this specimen is the appearance of decidual cells within the walls of the smallest blood vessels within the ovarian cortex in the close vicinity of the decidual tubercles mentioned above. Most of the microscopic sections show this change within the vessel walls, though the decidual tubercles appeared in sections of a small portion of the ovary.

Since grossly the ovary was the seat of a pregnancy, since the tube on the same side did not show any fetal elements, and since, further, the ovary was undoubtedly connected to the uterus by the utero-ovarian ligament, and lastly, since the chorionic elements were found microscopically in the blood clot, immediately surrounded on all sides by ovarian cortex, the diagnosis of ovarian pregnancy seems absolutely certain, and satisfies all the criteria laid down by Spiegelberg, Williams, Norris, and others.

The ovary measured about 6.5 x 4.5 x 2.5 cm.

Discussion.

Dr. Norris asked Dr. Rubin whether any serial sections were made of the ovary.

Dr. MacCallum: The most interesting point in this connection is the behavior of the corpus luteum. In a case seen last year in which the ovarian pregnacy was very definitely determined, the formation of lutein tissue was quite striking throughout both ovaries, and it seemed possible that since the follicle in which pregnancy was going on could scarcely carry on a normal formation of corpus luteum, similar tissue was formed in an unusual degree in other parts of the ovaries.

Dr. Rubin said that he did not make serial sections but cut out sections of various parts of the ovary. He preserved the ovary so that it could be demonstrated at future times.

DEMONSTRATION OF A CASE OF HEMOCHROMATOSIS.

A. M. PAPPENHEIMER, M.D.

The case is one from Dr. Janeway's service, and I am indebted to him for permission to report the clinical data. The essentials of the history are as follows: Man 37 years of age, alcoholic, had taken ten or twelve whiskeys a day. He became ill in March, developing symptoms of an acute diabetes with 4 to 7 per cent. of sugar in his urine. The liver was enlarged. There was rapid loss of weight, acidosis developed and the case terminated with high fever and symptoms of general infection. There was not noted, during the time the case was observed clinically, any striking pigmentation of the skin, but at the autopsy the skin is described as having a slight leaden hue and there were noted some patches of pigmentation, resembling freckles, on the surface of both forearms.

The autopsy was performed by Dr. Hanes, from whose protocol I abstract the following notes: On opening the abdominal cavity there is found an excessive amount of free fluid of dark-yellow color, and rather turbid. Adhesions about upper lobe of spleen and left lobe of liver. Heart and lungs practically normal. Spleen greatly enlarged, weight 570 gms., measuring 16 x 11 x 5½ cm., firm; there was a thick yellow deposit on the capsule. On section it was smooth, with no bulging of the pulp. There was no marked change in the color. The liver was large, weighed 2580 gms. The color of the liver was exceedingly striking; both on the surface and on section it presented a very typical, chocolate or bronze color characteristic of the affection. It showed a fine diffuse cirrhosis and a number of whitish foci, some with central softening, which proved to be abscesses or areas of necrosis. The stomach mucosa was considerably congested; it showed no striking pigmentation, although the mucosa was very thick and velvety. The rest of the intestinal tract showed nothing remarkable. Kidneys negative. Bladder negative. Perigastric and retro-peritoneal lymph-nodes and the pancreas showed the most extreme macroscopic changes, the cut sections presenting the typical chocolate or mahogany brown appearance. The pancreas was very firm, but neither enlarged nor atrophic.

Microscopic Examination.

Skin: One of the small pigmented spots on the chest was taken for examination. The Malpighian layer of the epidermis is free from pigment, but there is an abundant deposit of yellow granules giving the iron reaction, about the basement membranes of the sweat glands. The glandular and duct epithelium itself is free. This is a rather striking exception to the general rule that the pigment is deposited primarily in the glandular epithelium.

Liver: The liver lobules, which are of large size and irregular shape, are separated by stout fibrous septa, in which are many new-formed bile ducts. The liver cells stain well, and for the most part show no degenerative changes. They contain, without exception, masses of yellowish pigment granules giving the "hemosiderin" reaction, and showing a characteristic distribution in the distal supra-nuclear portion of the cells—away from the blood capillaries. The nuclei themselves are invariably free from blood pigment. In the interlobular connective tissue, the pigment lies in part within the connective tissue cells, in part scattered between the hyaline fibrils. The endothelial cells of the capillaries and of the larger vessels as well, contain it, as do the epithelial cells of the new-formed bile-ducts. The larger bile-ducts are relatively free.

The large abscesses are composed of necrotic material with much chromatin dust, pycnotic material and, at the periphery, a loose granulation tissue in which are numerous lymphoid and plasma cells. There is considerable iron-reacting intra and extra-cellular pigment scattered through the necrotic areas, and in places, the persitent liver framework is encrusted with iron salts, staining also with hematoxylon. To this peculiar incrustation, we shall refer again.

Pancreas: In this organ, also, there is a very pronounced sclerosis, which is both inter and intra-lobular in type. The pigment is extremely abundant, both within the parenchymal cells and in the stroma. Here, as in the liver, there is a distinct tendency for the pigment to be massed in the inner portion of the acinal cells, surrounding the lumen. The larger pancreatic ducts contain little or no pigment.

Very few islands of Langerhans were found in the sections examined. None of those discovered show marked fibrosis or hyalin change. Some of the island cells contain a good deal of coarse pigment, others are entirely free. On the whole, the islands contain decidedly less pigment than the acinal portions of the gland.

Adrenal: Here the pigment is virtually limited to the extreme outer portion of the zona glomerulosa, rarely extending a short distance into the fasciculate zone. The capsule is entirely free, and the pigment granules are apparently situated within the parenchymal cells, and not in the stroma. A few scattered pigment-bearing cells are found also in the medullary portion of the gland about the central vein—whether within chromaffin cells or not, it is difficult to say.

Spleen: Is congested. In the sinuses are many large endothelial (?) cells, with stippled protoplasm and small, deeply staining, eccentric nuclei. Many of these cells contain a few greenish-yellow pigment granules of small size.

The Malpighian bodies are small; the central artery is slightly sclerosed.

The trabeculae are not much thickened, but in many of them are irregular fibers staining bluish with hematoxylin, but giving a pronounced iron reaction with Perl's method. Under the immersion, the elastic fibers may be traced directly into these blue-staining fibers; one gets the impression, however, that the blue-staining material is deposited upon or along the refractile fibers, and one may occasionally follow an elastic fiber as a refractile central core, directly through the bluish portions. Some of the small blood-vessels are also wholly or incompletely converted into thick, rigid, blue-staining rings. The incrustation involves practically the entire muscular coat as well as the elastic fibers.

Lymph-nodes: Corresponding to the gross appearance, there is an enormous deposition of pigment in the mesenteric and peri-pancreatic lymph-nodes. In contrasting sections stained according to Perl's methods with those treated after Nishimura, with ammonium sulphide, followed by potassium ferrocyanide and HCl, one finds that the latter show an even greater amount of iron reacting pigment. The granules occur intra-cellularly, particularly in the endothelial cells of the lymph-sinuses, in giant-cells, and in free clumps between the cellular elements. There is a fairly marked fibrosis of the glands.

A very remarkable feature is the conversion of the reticulum in places into a dense, rigid framework which in part appears as a greenish refractile substance, in part stains a deep blue with hematoxylin. In places, these incrusted fibers have fragmented into short, thick bars, many of which are surrounded by large, foreign body giant cells, containing a dozen or more nuclei.

With the iron stains, the incrusted reticulum yields an intense blue color. Treated with a silver nitrate solution, a part at least of the reticulum stains black after exposure, demonstrating the presence of phosphates. Although the avidity of these structures for the hematoxylin as well as their refractile appearance in unstained sections, strongly suggested the presence of calcification, it was found that after treatment with a strong oxalic acid solution, they no longer stained with aqueous hematoxylin. This applies also to the incrustation of the walls of the small arteries, which showed the same lesion as those in the spleen.

One further feature is worth recording, namely, the occasional presence within the giant-cells of peculiar stellate inclusions, similar to those described and pictured by Wolbach (*J. of Med. Res.* Vol. XXIV., No. 2, 1911) and more recently by Vogel in a case of Bronchiolitis obliterans (*Virch. Arch.* Bd.

206, Hft. 1, 1911). These inclusions do not give the iron reaction, nor stain directly with the orcein elastic tissue stain.

Myocardium: The pigment is abundant. It shows a tendency to be massed about the poles of the nuclei in the undifferentiated sarcoplasma, but rows of granules extend also a considerable distance between the fibrillae. The interstitium is practically free from pigment.

Stomach: In the gastric mucosa, there is a fairly abundant deposit of pigment in the depths of the glands. The more superficial layer of the epithelium as well as the muscularis, is quite free. One observes again the tendency of the pigment to accumulate in that portion of the secreting cell which is next to the lumen of the gland tubule and away from the basement membrane. This is very distinct in cross sections, where the lumen is seen lined with blue granules.

From the above report, it is evident that the case is a very typical one, resembling closely, both in the clinical and pathological features, many of the previously observed cases. The conflicting and inadequate theories regarding the pathogenesis of the disease, have been excellently summarized by Sprunt in a recent article (*Arch. of Int. Med.*, Vol. 8, No. 1, 1911), and need not be discussed here. The features of particular interest in this case are, perhaps, the absence of noteworthy changes in the islands of Langerhans, in spite of the intense glycosuria, and the remarkable iron incrustation of the elastic and reticular fibers of the lymphnodes and splenic trabeculae.

(Sections of the organs above described were demonstrated with the projection apparatus.)

Discussion.

DR. EWING: In a case of hemochromatosis examined by Dr. Elser, of the New York Hospital, some years ago, and used in our laboratory for class demonstration, the pancreas differed essentially from that described by Dr. Pappenheimer, in that it showed an enormous increase in the number and size of the islands. These occupied in some places at least half of the parenchyma.

Dr. Libman: About six or seven years ago we had a very interesting case of diabetes in which at post-mortem examination we found marked hemosiderosis of the liver and spleen, but none of the pancreas. There was present a hyaline degeneration of the islands of Langerhans. We considered this case of some importance because it demonstrated that the explanation given by certain authors of the pathogenesis of bronzed diabetes cannot hold in all instances. According to these authors, there is first a hemosiderosis of the pancreas, and later a cirrhosis of the pancreas, this leading to a glycosuria. In the case which I have mentioned, this could not hold true.

CARCINOMATOUS INFILTRATION OF THE SOLAR PLEXUS.

ELY MOSCHCOWITZ, M.D.

J. S., 48 years old. The esential facts in his clinical history are these: Gradually increasing jaundice of fourteen months duration accompanied by a gradual loss of weight. For the past four weeks, attacks of pain in the abdomen, which were relieved by catharsis. Physical examination, with the exception of a deep jaundice, was negative. At exploratory operation, the pancreas was found enlarged; a few small nodules on the upper surface of the liver were noted, one of which was removed and from a frozen section was reported adeno-carcinoma. A cholecystectomy was done. The patient died 24 hours later.

The autopsy was incomplete. A firm mass was found lying above the pancreas and surrounding the superior mesenteric artery. The mass was irregular in outline, densely adherent to the pancreas, firm and grey. Superiorly it merged gradually into the surrounding retro-peritoneal tissues. On section, small cone-shaped projections are distinctly visible upon pressure, which recede as the pressure is released. Numerous smaller and larger bile stained glands are present, within and surrounding this mass.

The primary tumor was apparently not removed at autopsy, but was probably situated either in the terminal portion of the biliary passages or in the duodenum. The condition of the remaining organs at autopsy is indicated by the *Anatomical Diagnosis:* Obstructive Jaundice. Metastatic Carcinoma of the liver and pancreas. *Interstitial pancreatitis.* Dilatation of the gall-bladder: fresh cholecystectomy; Periportal cirrhosis with fatty degeneration and bile pigmentation of the liver. Hyperplasia and chronic congestion of the spleen. Fatty and parenchymatous degeneration of the kidneys.

Microscopical Examination.

The nodules of the *liver* showed typical adeno-carcinoma. The organ otherwise shows chronic congestion and slight periportal cirrhosis.

Spleen: Chronic congestion. *Kidneys:* Chronic diffuse nephritis. *Pylorus and portion of duodenum removed:* Negative. *Pancreas:* There is a marked cirrhosis with an abundant increase in the peri-acinar and interlobular connective tissue. There is much round-celled infiltration. The acini are distorted in shape, due to the growth of the peri-acinar connective tissue. Numerous islets of adeno-carcinoma are present in the interlobular connective tissue, especially in the head of the pancreas. The connective tissue around the biliary passages shows a number of islets of adeno-carcinoma. The nerves in this situation show infiltration with adeno-carcinoma similar to that about to be described.

The mass lying above the pancreas consists of numerous nerve bundles and connective tissue, fat, areolar tissue and lymphatic glands. It is apparent from the relations of this mass to the pancreas and the superior mesenteric artery that the collection of nerve bundles constitutes in the main the superior mesenteric or solar plexus.

Only a small minority of the nerve bundles have escaped carcinomatous invasion.

The majority of the nerves show a carcinomatous infiltration, which is distributed in three ways.

1. The carcinoma is strictly limited to the perineurium. (Fig. 1).

2. The carcinoma is strictly limited to the endoneurium. (Fig. 2).

3. Both perineurium and endoneurium are involved. (Fig. 3).

In many instances, there is evidence of continuity between the perineural and endoneural carcinomatous acini, and between the perineural invasions and small infiltrations lying just outside the perineurium. The epineurium otherwise is remarkably free from carcinomatous invasion.

The nerve bundles are very large and show areas of degeneration, more or less complete.

Tumor invasion of the sympathetic plexus is uncommon. The majority of the cases, thus far reported, involve the hypogastric plexus, usually following cancer of the uterus. A rather thorough search of the literature fails to reveal a hitherto reported case of cancerous involvement of the solar plexus.

To explain the peculiar distribution of the cancerous invasion in this case, a study of the anatomical distribution of the lymph spaces of the nerves, as elucidated by Axel Key, and Retzius, Ranvier and Waldeyer, offers illuminating information. These authors showed that the lymph spaces of nerves are in direct communication with the subarachnoidal and subdural spaces and can be injected from these situations. They found that the lymph spaces of the nerves are arranged concentrically in the perineurium, from which they pass directly into the endoneurium and from here around each nerve fibre, so that each fibre is bathed, as it were, in lymph fluid. In no instances could any communication be discovered between these lymph spaces and the lymphatics of the nerve trunk, which run in the epineurium.

With these facts in mind, we note how closely the cancerous infiltration in the case just reported simulates the distribution of the lymph spaces. This case may therefore be regarded as a pathological demonstration of the anatomical distribution of the lymph spaces of nerves.

The perineurium may therefore be regarded as a protection against invasion from the lymphatics externally to it. This explains the comparative immunity of involvement of the nerve bundles in carcinoma of the peripheral trunks of nerves and in infectious lymphangitis. It also explains the selective distribution of the toxins to the nervous system in tetanus.

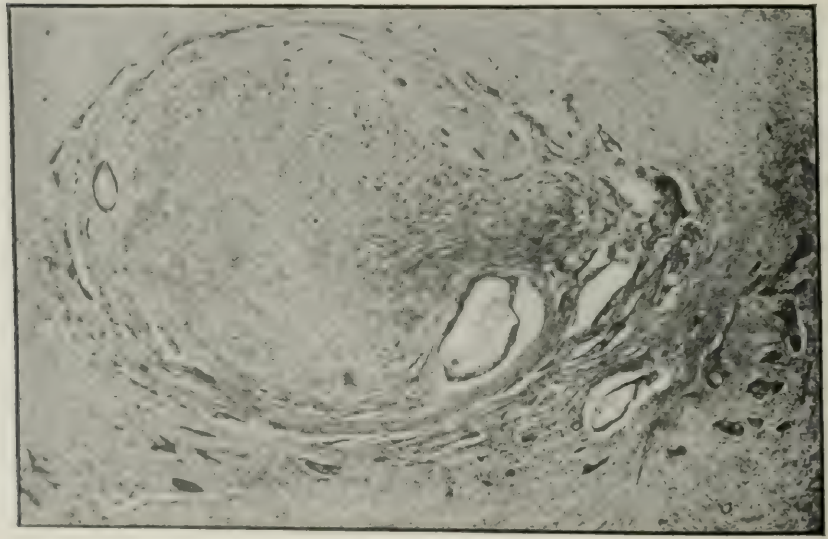

Fig. 1.—Showing Perineural Invasion by Carcinoma.

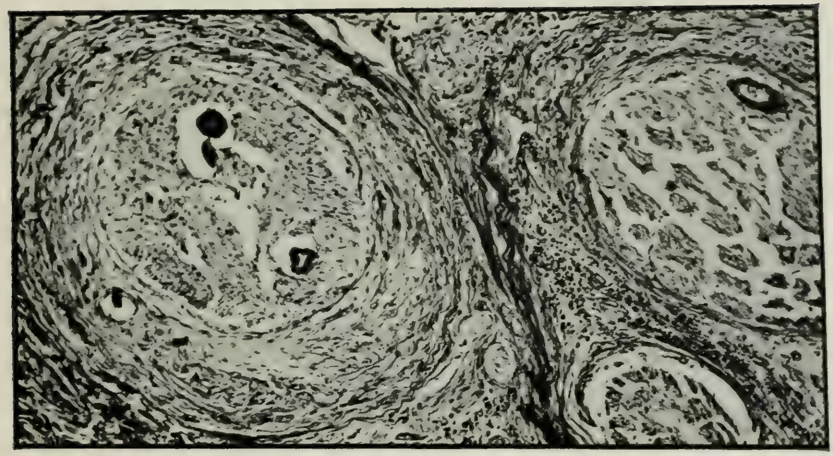

Fig. 2.—Showing Endoneural Invasion by Carcinoma.

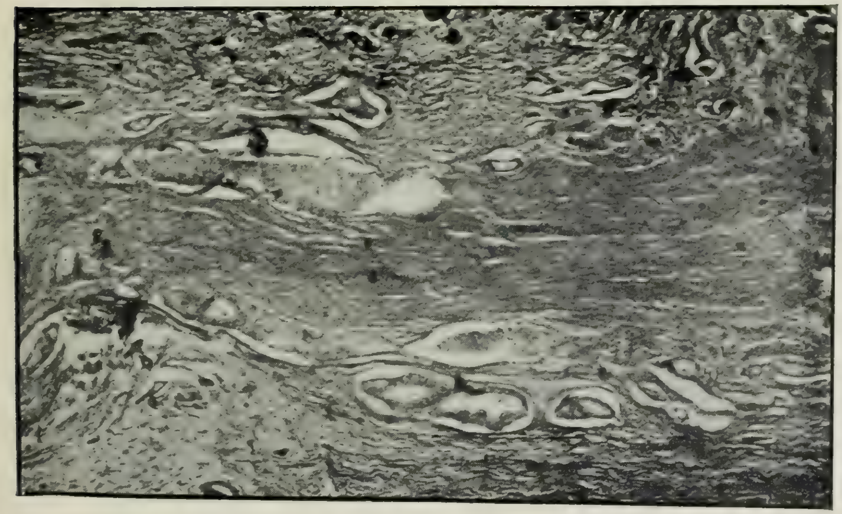

Fig. 3.—Showing Perineural and Endoneural Invasion by Carcinoma.

PRIMARY THROMBOSIS OF SUPERIOR MESENTERIC VEIN.

JAMES EWING, M.D.

Patient, male, 55 years of age, of temperate habits, without history or external signs of lues, and while apparently in excellent health, was suddenly seized with sharp pain in the lower lumbar region. The pain grew more severe and he was soon prostrated. Twelve hours later there was moderate general abdominal tenderness but no localized tumor. The bowels moved once moderately and the feces were decidedly acholic but apparently free from blood. No fever. Leucocytes 25,000, 80 per cent. polynuclear. This condition continued for 48 hours without definite change, but the pulse was notably weak from the first. On the third day there was a sudden turn for the worse with vomiting, collapse, and signs of peritonitis, and the patient died 72 hours after the first symptom. For this abstract of the history I am indebted to Dr. C. L. Gibson.

Necropsy.

Body of well-nourished male. Line of pubic hair ceases at pubes. General pilosity slightly below average. There are no other signs of Status Lymphaticus. No external markings. Slight jaundice. No oedema. Rigor moderate. Subcutaneous fat well developed. Abdomen slightly protuberant.

Blood cultures taken from right median basilic vein proved sterile on blood agar and plain agar, aerobic.

The peritoneal cavity contains about a pint of blood-stained fluid. A portion of small intestine measuring 177 c.m. in length occupying the intermediate portion of the lower ileum is black and infiltrated with blood. The peritoneal surface over this area is granular. The tissue is firm from distension of vessels. Its position is normal and none of the coils is confined by adhesions of any kind. It occupies the mid-abdominal region and presents beneath the omentum which is freely movable over the infarcted coils.

The entire mesentery leading from these coils is thickened and firm and the course of many vessels may be palpated as firm thrombosed cords. In the region of the pancreas there is a tumor-like mass in the root of the mesentery which on removal and incision proves to be the main mesenteric vein and branches, which are thickened, dilated and filled with a firm lamellated thrombus. The thrombus terminates above in a firm elongated free extremity at the level of the upper border of the pancreas. At this point also the wall of the vein is covered by a thin firmly adherent parietal thrombus (Adhesive Thrombophlebitis). Below, the thrombus is continuous with the black blood masses in the mesenteric border. The mesenteric artery is empty and contracted. The intestinal contents consist chiefly of dark, bloody fluid. The intestinal mucosa is dark, necrotic. On lifting the infarcted intestine out of the abdomen, it breaks apart near the center of the infarcted area.

An old thin fibrous band binds the coecum to the right side of the false pelvis. The appendix is normal.

Pancreas: Firm, hard, light colored.

Liver: Surface slightly irregular, mottled light areas with lines of deep congestion. Gall bladder contains a little bile. No calculi.

Stomach appears normal externally.

Kidneys: Size and consistence normal. Capsule strips, surface slightly granular. Markings somewhat irregular.

Adrenals: Normal.

Spleen: Large, soft, and very dark.

Remaining organs not examined.

Anatomical Diagnosis.

Primary thrombosis of mesenteric vein.

Infarction and necrosis of ileum. Beginning peritonitis.

Cirrhosis of liver.

Microscopical Examination.

The mesenteric vein from above the pancreas down to its bifurcation is the seat of an advanced productive inflammation.

All the coats of the vessels are involved, especially the media and intima. The adventitia is infiltrated with round cells, and new fibrous tissue, new vessels and round cells extend well out into the surrounding fat tissue. The media is much thickened with many collections of round cells, many new capillaries and much new fibrous tissue, new vessels and round cells extend well out into the surrounding fat tissue. The muscle bundles are atrophic and widely separated by oedema and hyaline connective tissue fibrils. The intima shows large areas of fibrous thickening. The lumen is occupied by a firm adherent mixed thrombus, in places containing many polynuclear leucocytes. The thrombus is adherent at many points along the main venous trunk. At several points there is beginning organization going out from the eroded intima. Where the vein comes in contact with the pancreas there is a saccular dilatation, the wall of which is very thin. The adjoining area of the pancreas is the seat of advanced interstitial productive pancreatitis.

The peripheral branches of the mesenteric vein down to the intestinal border are distended with blood in which there is little fibrin, while the vessel walls are not altered. Portions of the thrombosed mesenteric vein were stained by Levaditi's method for spirochaeta pallida, and although a prolonged search was made no spirochaetae were found.

The splenic vein is varicose, but the thrombus ends sharply at its junction with the mesenteric vein.

The mesenteric artery shows marked mesarteritis, with fibrosis, atrophy of muscle fibres, and many small mucous or fatty cysts.

The infarcted intestine is completely necrotic. Elsewhere the vessels are distended with blood. No old lesions were discovered in the intestines.

Pancreas shows moderate fat invasion. In many lobules there are areas of dense old fibrous tissue. There is no fat necrosis and the ducts are pervious. The pancreatic parenchyma is normal.

Liver shows distension of portal veins and occasional areas of fatty infiltration. The portal canals are often much thickened and infiltrated with round cells, especially about the portal veins.

Kidneys: There is well marked arteritis of the interlobular arteries; a few glomeruli are atrophied, but most of them are normal. The tubule cells are slightly degenerated.

Microscopical Diagnosis.

Mesenteric Thrombo-phlebitis.
Hemorrhagic infarction and necrosis of Ileum.
Chronic interstitial pancreatitis.
Arteritis of renal vessels.
Cirrhosis of liver.

Summary.

The study of the lesions in this case shows with entire certainty the course of events that led to the patient's death. A long established inflammation of a considerable portion of the mesenteric vein led eventually to a parietal thrombosis of this vein, beginning near the pancreas. This partial occlusion of the vessel led to venous stasis in the intestine, with pain and prostration. The parietal thrombus soon became complete during the 48 hours of the illness, and this was followed by complete strangulation and necrosis, which proved rapidly fatal.

The thrombosis is fully explained by the changes in the wall of the upper few inches of the vein, and there is no need to look for primary lesions in the intestine, which were found to be missing. The main thrombus was old (3 days), firmly adherent, and lamellated, the peripheral veins being gorged with blood without coagulation.

The cause of the phlebitis is not clearly indicated in the histological appearance of the lesion. The blood being sterile, there was no indication of general septicemia with local vascular lesions.

The commonest cause of localized chronic phlebitis is syphilis, and the lesions were somewhat similar to those which occur in syphilis. As possible additional signs of syphilis there were old periportal cirrhosis of the liver, interstitial pancreatitis, and renal arteritis. Yet none of these lesions is pathognomonic of syphilis, and together they are inadequate to establish the diagnosis of syphilis. After syphilis, general arteriosclerosis suggests itself as the true explanation of the conditions disclosed. From this point of view one may attribute all the lesions found in the body to deterioration in the structure of the vessel walls with secondary changes in the organs. The changes in the liver and kidney seem most reasonably explained in this way rather than by syphilis. These lesions lack the pronounced character that one expects in syphilis, and seem to be chiefly degenerative with subsequent new growth of tissue. For the advanced stage of the lesion at the mesenteric region a special factor is needed, for which one might suggest a special congenital weakness of the vessels at this point. The splenic vein was unusually thin and tortuous. Or some special factor might be found in the patient's alimentary history. Therefore I would offer as the most probable explanation of the case: Arteriosclerosis of complex origin, not syphilitic, acting with special intensity on congenitally weak mesenteric vessels.

Study of the Literature.

The study of the literature serves to place the present case in its proper series among the forms of mesenteric thrombosis, and throws some light on the etiology.

Lissauer (*Virchow's Archiv.*, 1908, Bd. 192, p. 278) made an exhaustive study of 68 cases examined at autopsy in Breslau. He was able to find adequate causes of this condition in 92 per cent. of the cases as follows:

	Per Cent.
Cirrhosis of the liver	9
Syphilis of liver and mesenteric vessels	10
Cancer of liver	6
Cancer of stomach	10
Cancer of gall bladder	9

Gall stones (suppuration)	13
Diseases of pancreas	15
Diseases of spleen	7.5
Appendicitis	9
Intestinal cancer	3
Suppuration of navel	1.5
	92

In all but nine of the cases the etiology was clear, but in these nine there was no gross alteration in the vessel wall. In six of these nine cases the thrombosis was attributed to cirrhosis of the liver, and in three no definite etiology was established. In none of the nine doubtful cases was there a microscopical examination of the vessel wall. From this study it does not appear that primary thrombosis of the mesenteric vessels can occur without local lesions in the vessels, nor do I find that the old idea of a spontaneous thrombosis in the mesenteric vessels has any definite support in recent literature.

Our case certainly belongs in the group caused by primary phlebitis. Borrmann (*Deutsch. Arch. kl. Med.*, 1897, Bd. 59) discusses this group at length, reporting seven cases, in all of which he considers a luetic origin practically certain on account of the structure of the lesions and the presence of well marked sclerosis of the liver. The present case showed a phlebitis resembling a syphilitic lesion and peculiar cirrhosis of the liver, which might be syphilitic, and Borrmann would, therefore, probably have called it luetic.

As other possible causes of local productive phlebitis, Borrmann mentions old age, high arterial pressure, and alcoholism.

Our patient was not old, had no signs of Bright's disease, and was not alcoholic.

From this point one is reduced to references to clinical reports of diseases preceding primary mesenteric thrombosis and to other general causes of chronic productive phlebitis. Sprengel (*Arch. fur kl. Chir.*, Bd. 67, p. 587) analizes several cases from this point of view. In one there were varicose veins in the legs. Our patient had a varicose splenic vein but no others, and this was probably connected with the mesenteric phlebitis. In three other cases, typhoid fever, severe diarrhoea, and pneumonia preceded the thrombosis by a few weeks or months, but our patient had none of these diseases.

Jackson, Porter and Quinby analize over 200 cases (*Jour. Amer. Med. Assoc.*, 1904, Vols. 42, 43). They find many cases of primary productive phlebitis, some of which were clearly syphilitic, but they do not discuss other sources of such phlebitis.

Deckart (*Mittheil a. d. Grenzgeb. d. Chir.*, Bd. 5, 511) analizes 67 cases of mesenteric arterial or venous thrombosis, and cannot decide why, in some cases, there is anemic infarction and in others hemorrhagic infarction of the intestine. The result does not apparently depend on which vessel is involved.

The frequency of primary mesenteric thrombosis high up in the superior mesenteric vessels suggests that this may be a weak point in the anatomical structure of the vascular system in certain subjects. At this point the large splenic vein receiving pancreatic and gastric branches unites with the superior mesenteric to form the portal vein. Here is a remarkable juncture of large veins draining the organs of digestion, and more or less influenced by changes in the position and function of these organs. It would seem reasonable to suppose that primary inflammation of the vessels at this point might occasionally result from traumatism, over-distension, irritation by digestive products, or from premature senile changes. A luetic origin need not be assumed for every case of primary productive arteritis or phlebitis, especially in this region.

In the present case, as in some of Borrmann's, all of the organic lesions might be referred to slowly advancing senile changes in the organs and vessels.

Borrmann and others fully recognize the necessity of recognizing arteriosclerosis with its complex etiology, as a prominent cause of mesenteric phlebitis and thrombosis. The present case seems to fall in this category.

A LARGE TUMOR OF THE LIVER, ASSOCIATED WITH A TUMOR OF THE OESOPHAGUS.

CHARLES NORRIS, M.D.

The liver and oesophagus which I show you came from a man 73 years old, with very little clinical history, except that he had been, up to middle age, a severe drinker, and three months before death he had epigastric pain and lost weight and became very weak.

At autopsy there was found a very large liver which practically occupied the right half of the upper quadrants of the abdomen. A clinical diagnosis of primary carcinoma of the liver had been made and, before I came across the tumor of the oesophagus, it seemed to me that that was a likely diagnosis, the tumor resembling some of the cases of primary carcinoma of the liver that I have seen. An interesting observation in this case is that, although the metastatic growth in the liver was so extensive, there were no metastases elsewhere with the exception possibly of one, say only 3 or 4 mm. in length by one mm. in breadth, on the pleura of the left lower lobe of the lung. No metastatic nodules were found in the other organs on microscopic examination.

The tumor in the oesophagus is situated at the bifurcation of the trachea, measuring 7 cm. in length by 3 cm. in breadth. About 1 cm. of the wall of the oesophagus is free from growth. There is no stenosis of the oesophagus. The portion of the trachea beneath the tumor of the oesophagus is uninvolved, the mucous membrane being normal in the gross.

The growth in the liver and oesophagus were identical as to their histology. I am unable to make up my mind, for the present, whether to call the tumor an epithelioma or a sarcoma.

Discussion.

Dr. James Ewing: I had an opportunity to study these specimens in the gross and microscopically, and I came to the conclusions (of which I am not entirely certain) that Dr. Norris' interpretation is correct and that he is not dealing with primary carcinoma of the liver.

A more difficult point to decide is the true nature of the tumor. But, all things considered, it seems to me the chances are very much in favor of its being an embryonal epithelioma—it does not seem to me probable that a tumor in the liver of this sort could have reached the oesophagus in the region where we find this ulceration. The ordinary epithelioma of the oesophagus, however, show a tendency to extend toward the stomach and liver.

As Benecke has shown recently, some of the supposed implanted metastases of carcinomata in the stomach are to be explained as a result of extension through the lymphatics to the submucosa of the stomach, where they sooner or later protrude in the form of a flat tumor or ulcer.

The remarkable cell characteristics of this tumor are extremely interesting, but I think they suggest that the tumor has arisen from some embryonal group of cells in the oesophagus.

I ought to apologize for offering this somewhat positive opinion in the presence of Dr. Norris, who has studied the case more thoroughly than I have, but I know he was of this opinion up to recently and I think he can safely retain his original diagnosis.

SPECIMENS FROM A CASE OF BISMUTH POISONING.

GEORGE BAEHR, M.D.

Before showing the specimens from a case dying of bismuth poisoning, it is only necessary to mention a few points concerning the clinical course. The patient was a man 19 years of age, who one year before admission to the hospital had sustained some injury to his left hip. Following this he developed three suppurating sinuses, two of which were superficial and one deep. After entering the hospital he was operated upon, the two superficial sinuses excised and the wound closed with sutures. The following week an attempt was made to dissect out the third sinus, but it was found to be too extensive. It was, therefore, decided to use Beck's paste injections as treatment. Three ounces of a 24½ per cent. suspension of bismuth subnitrate in vaseline were injected into the sinus. Five days after injection, the patient complained of salivation and sore gums. On the seventh day his gums showed a line resembling very closely a "lead" line, and two days later the patient developed a small ulcer under the tongue, which gradually spread along the course of the ranine vessels. Two weeks after the injection, he developed a large ulcer on both tonsils, which spread rapidly to the faucial pillars, soft palate, uvula and pharynx. It was of a dark grayish-brown color. The patient's breath at this time had a very foul odor, but not like that of tellurium, at one time a not infrequent impurity in bismuth salts. Three weeks after admission the blood picture was normal, except that it showed a secondary anemia and a marked stippling of the red cells, an observation which has not been described in any previously reported case of bismuth poisoning. Three weeks after the injection of the bismuth the patient developed a diarrhoea which became very marked, progressive anemia and emaciation, and died three weeks after the injection.

At autopsy, in addition to relatively insignificant parenchymatous changes in the various viscera, there was found an intense parenchymatous degeneration in the kidneys, which has been described in other cases and which is only equalled in cases of bichloride poisoning. The intestines showed a remarkable lesion. The mucosa from the ileo-caecal valve to the anus and including the terminal four inches of the ileum was completely necrotic, markedly thickened, and of a grayish-black color.

With microchemical tests particles of bismuth were not detected in any viscus. On gross analysis, however, the liver, spleen, kidneys and large intestine showed the presence of large quantities of bismuth and of no other heavy metal except iron.

The microscopic examination of tissues removed from side of the wound showed a very interesting condition. Large quantities of bismuth particles could be demonstrated by microchemical means in phagocytes in the wall of the sinus. These phagocytes filled with small particles of bismuth were to be seen invading the deeper tissues and even the muscle, suggesting a mode of entry of the bismuth into the body.

Discussion.

Dr. Larkin: Because of the close resemblance of the lesions described to those caused by bichloride of mercury, Dr. Larkin wished to know whether the chemical examination had included a search for mercury or arsenic. He rather questioned the probability of an innocuous substance, such as bismuth subnitrate, causing such extensive lesions.

Dr. Frank: There are quite a number of cases on record where after the injection of Beck's paste, bismuth poisoning has developed. There is no question but that quite incontestable cases have occurred.

Dr. Baehr: Not only was the Beck's paste carefully analyzed for other metals (lead, arsenic, antimony, zinc and mercury), but the urine, stools and all the viscera were similarly analyzed and nothing else found besides the bismuth which could possibly produce the picture. The urine and stools throughout the clinical course also contained large quantities of bismuth. Beck advises washing out the sinus with olive oil; but in this case it proved of no avail. It has been suggested that the intestinal lesion resembles that of bichloride poisoning. This must be admitted. But the line on the gums in this case resembled the "lead" line, but that does not make the condition lead poisoning.

It surprises me that the pathogenesis of this condition should be questioned. Merck's chemically pure bismuth, which upon subsequent analysis was proven to be chemically pure, was injected into the sinus. Considerable quantities of bismuth but of no other heavy metal were recovered from the liver, spleen, kidneys and large intestine post-mortem.

Concerning the remarks of one of the gentlemen, relative to the conception of bismuth subnitrate as an innocuous substance, I desire to report that during the past few months at Mount Sinai Hospital we have had the opportunity of observing two other cases of bismuth poisoning which recovered. Complete details of these two cases and of the case under discussion this evening will be published shortly by Dr. Mayer and myself.

Poisoning by bismuth is not rare. The literature contains reports of almost seventy undoubted cases. When administered by mouth the poisonings have chiefly occurred in young children in whom, because of decomposition of the subnitrate by bacteria, the symptoms have been those of nitrate poisoning. The majority of instances of bismuth poisoning have followed injections into sinus cavities, and nearly all of these have been entirely due to the bismuth radical.

Experimentally, extensive work has been done to prove definitely the toxicity of bismuth. The most important has been done by Meyer and Steinfeld and by Schmelzer. The latter did his work in Kobert's laboratory and Kobert, in his book, has accepted this work as conclusive. The lesions in the intestines, obtained by Meyer and Steinfeld, in some of their experiments, correspond in most details with those shown this evening. In fact, of the cases of bismuth poisoning coming to autopsy that have been reported, this one corresponds most accurately to the results obtained in most of the experimental work.

DEMONSTRATION OF THE CARDIAC LESIONS OF SUBACUTE BACTERIAL ENDOCARDITIS.

E. LIBMAN, M.D.

My object in showing you this collection of hearts to-night is fourfold. The main reason is that I believe that Dr. Baehr's demonstration of the glomerular lesions of subacute bacterial endocarditis will be made clearer if you at the same time see the cardiac lesions. The second object is that I want to demonstrate that the lesions in the cases in which the mitral valve is involved are quite characteristic of the infection by the attenuated coccus found in most of these cases. Thirdly, I hope to convince you that there are three stages of the disease in a number of the cases—the bacterial, abacterial healing, and abacterial healed stage. In the fourth place, I would like to point out to you that at least some of the cases which we have been wont to call "chronic endocarditis with fever" are examples of the healed form of the disease. For healing from a pathological standpoint does not necessarily remain recovery from a clinical standpoint.

The term "subacute bacterial endocarditis" I have adopted instead of the older terms: "chronic ulcerative endocarditis," "chronic malignant endocarditis," "chronic infectious endocarditis," etc. I call all cases of endocarditis which are proven due to bacteria (rheumatism is not so proven) "bacterial endocarditis" and divide the cases into "acute," "subacute," or "chronic," according to their clinical course. Many of the cases that belong in the group of which we are speaking to-night last only four to six months and are, therefore, certainly subacute and not chronic. Some may prefer to apply the term "chronic" to cases that last over one year.

We have had the unusual advantage of seeing a very large number of cases of the disease under discussion, and in 64 cases in which cultures were made during life, 94 per cent showed the attenuated cocci* ("streptococcus viridans" of Schottmueller).

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*See discussion of Dr. Larkin's presentation, at the November meeting, by E. Libman.

In three cases the influenza bacillus was found, and in one the gonococcus. Once the cocci were found in the vegetations postmortem, the cultures taken during life being all negative. Twice the cocci were found in the vegetations only, no cultures having been taken intra vitam. The gonococcus case does not properly belong in the group, as the case was of a rather acute type. It is included, however, for comparison, because the lesions in the heart were much like those characteristic of infections by the attenuated cocci.

In seven cases which we believe belong in the groups of subacute bacterial endocarditis, but which are in a healing or healed stage, the lesions were found bacteria-free. And of those cases among the seven in which cultures were made during life, they were negative.

(Dr. Libman now demonstrated the lesions in forty-one hearts belonging to the group.)

As you have seen, when the mitral valve is involved in these cases (and it is involved in the larger number of the cases), there is a tendency for the vegetations to spread upon the left posterior wall of the auricle, rather than on the valve edge. Very often the chordæ tendineæ attached to the posterior flap are covered to a greater or lesser extent by vegetations. Nearly always the anterior flap is also involved, and here the vegetations tend to grow down over the chordæ tendineæ, the involvement of the latter being often very extensive. Not uncommonly the chordæ tear, the torn ends being massed together by vegetations at the edge of the flap or the lower ends lying loose near the papillary muscles. The vegetations are yellowish, greenish, pinkish, or reddish in color, and vary much in size in different cases. As they grow older they become firmer and assume a more grayish color.

When the aortic valves are involved, the lesions are usually not characteristic and their extent is very variable. There may be only a small vegetative mass on one or more flaps. On the other hand, there may be enormous green masses that must block the orifice to a certain extent. The vegetations have a tendency to extend down over the endocardium at the position of the septum membranaceum, and over the ventricular aspect of the aortic flap of the mitral valve and down over the chordæ tendineæ. There may develop an aneurism of the aortic flap of the mitral valve. Ulceration of the aortic valves at times occurs.

The frequency of involvement of the valves, the left auricle, and the chordæ is as follows:

	Cases.
Auricle, mitral valve, and chordæ	17
Auricle, mitral valve, chordæ, and aortic	5
Auricle and mitral valve	2
Mitral valve and chordæ	1
Aortic valve only	3
Aortic valve, chordæ, and oartic flap of mitral	4
Mitral, chordæ, and aortic	1
Auricle, mitral, and aortic	1
Total	34

The auricle was involved 25 times, the mitral valve 27 times, the chordæ 28 times, and the aortic valve 9 times. The frequency of the involvement of the chordæ and auricle is very striking. The lesions which we consider so characteristic in the group of cases, we have not found in a large series of cases of endocarditis due to the streptococcus, the pneumococcus and the staphylococcus. And, as in the present group of cases, most all are due to the attenuated cocci; the lesions must be considered characteristic of infection by these cocci. Other observers have noted similar lesions in small groups of cases I will discuss their observations in a later paper.

After I had made these observations, I found lesions in the case (which I now demonstrate to you) of a man who died with the clinical picture of uremia, which I considered to be the healed form of the lesions I had previously found in cases of infection by the attenuated cocci. There were, as you see, extensive healed lesions of the auricular wall, and the chordæ tendineæ attached to the anterior flap are torn, and are thickened, fibrous and in part calcareous. My opinion that these were healed lesions of subacute bacterial endocarditis (in all probability due to the cocci, as they cause most all of the cases) was confirmed recently by Dr. Baehr's studies of the kidneys, in which he found the pathognomonic glomerular lesions (in a healed state). Later I came across two further cases. On going through my collection carefully I found that partial healing occurs in many cases, and that partial healing can occur even while there are still bacteria in the blood.

Last summer I had a case in the ward that belonged clinically in the group usually called "cases of chronic endocarditis with fever." The clinical phenomena led me to suspect that the case was one of healed subacute bacterial endocarditis and that the continuance of the clinical phenomena was due to the fact that there was a large calcareous mass on the aortic valve from which pieces were continually breaking off, the calcareous mass representing the healing of a large mass of vegetation. At autopsy the conditions of the aortic valve was as suspected during life, and Dr. Baehr found pathognomonic healed glomerular lesions. I show you now specimens from two other cases of a similar nature which were in our collection, and which we now have proven by study of material from the kidneys, that they are instances of healed subacute bacterial endocarditis. One can not diagnose that a case is abacterial simply because the blood cultures are negative, for I have seen one case in which five blood cultures were negative and still the heart post-mortem shows a lesion which was at least in part active.

I now have under observation several clinical cases that I believe represent the healed form (from a pathological and bacteriological point of view) of the disease under question. I shall later report on the clinical picture and the diagnostic points. I may say now that some pass as cases of chronic nephritis complicating chronic endocarditis.

There is very little in the literature concerning the healing of this disease. Latham describes a case which recovered after a number of cultures had been positive. Reiche describes one such case which died of an aneurism of an intrahepatic branch of the hepatic artery, having had negative cultures after a number were positive. He states that the cardiac lesions were healed, but does not describe them. Osler, Horder, Rosenow and Schottmueller do not seem to have met with healing or healed cases. Lenhartz described two cases, but they were not followed up. After I had announced this demonstration, my attention was drawn to a paper by Harbitz.* He, in the extensive pathological study of endocarditis, found ten instances of what he thought represented healing forms of bacterial endocarditis.

Apparently many cases recover spontaneously. They must be short in duration, and have but few symptoms and are therefore not suspected of having any infection. Perhaps many such patients do not feel sick enough to call in a physician. The cases which we see with positive cultures do not usually recover. We do see cases become abacterial, but they usually die in a short time from embolisms, anemia, exhaustion, decompensation, or other causes. I had one patient with influenzal endocarditis, in whom three cultures were negative after five were positive. He died later of anemia and decompensation.

Discussion.

DR. LARKIN: I should like to ask Dr. Libman if all the cases of malignant endocarditis which he described to-night are those which have been implanted on chronic cardiac valvular lesions, or if he has seen any of the lesions in which the endocarditis coccus was implanted on previously normal valves?

DR. PAPPENHEIMER: I should like to ask Dr. Libman whether he believes that the lesion begins on the auricular wall and extends down to the valve? He mentions several specimens that show healing, in which the reparative process is most advanced on the auricular wall.

DR. MOSCHOWITZ: I should like to ask Dr. Libman whether he has been able to trace the source of infection?

**Deutsche med. Wochenschr.*, 1899.

DR. LIBMAN—Answer to DR. LARKIN: Nearly all of these infections occurred in valves that were previously diseased.

Answer to DR. PAPPENHEIMER: I am inclined to believe that the process begins near the free margin of the valve, and extends upwards on the auricular wall. In several instances the reparative process is most marked in the upper part of the lesion.

Answer to DR. MOSCHOWITZ: We have not yet made extensive studies on the source of infection. We believe that the organisms may gain their entry through the throat; English authors seem to think that the intestines represent the site of entry. The important point is that we had not hitherto recovered the attenuated cocci in the blood except in cases of endocarditis. And in none of these cases do we find an inflammatory focus anywhere in the body which represents the portal of entry. It is therefore important that one be very careful before instituting any operative procedures in cases in which these organisms are found in the blood, because foci which might clinically impress one as being a possible source of invasion, are really the results of embolic processes.

GLOMERULAR LESIONS OF SUBACUTE BACTERIAL ENDOCARDITIS.

GEORGE BAEHR, M.D.

It seems remarkable that such a distinct pathological picture as is present in this disease of the glomeruli of the kidney should have been almost universally overlooked. Clinically, it has been known to many observers who have had a number of cases of this disease, that hematuria was almost a constant phenomenon, at least microscopically, but usually interpreted as indicating a hemorrhagic nephritis. Lenhartz, for example, in his original paper and in his book in describing four cases of chronic bacterial endocarditis mentioned the occurrence, and Harbitz in 16 cases made a special point of the association of nephritis hemorrhagica with this disease. Similarly, Heubner, Romberg and Horder have made note of the almost constant occurrence of hematuria in this disease.

That the disease was not overlooked before Loehlein's original paper in which this lesion was described, is shown by the fact that Aschoff described a glomerular lesion which in some details resembled the one to be presently described, but which he included in the classification of acute glomerulo-nephritis. In speaking of the etiology of acute glomerulo-nephritis he mentions ulcerative endocarditis as one of the commonest cases. According to our experience, lesions of the glomeruli are ordinarily not present in the acute ulcerative endocarditis, and his cases were therefore probably chronic. Aschoff does not, however, associate the glomerular lesion with his cases of chronic "ulcerative" endocarditis.

In Loehlein's original paper on inflammatory diseases of the glomeruli, the same type of glomerular lesions which forms the subject of this presentation was described, but was classified by him in his group of subacute glomerular nephritis, although he noted some essential differences and noted that in both instances the individuals in whom the lesions were found suffered from chronic ulcerative endocarditis. At that time he thought the lesion due to some toxin of the disease. He redescribed these cases in 1910 and added six others, considering them as a distinctive type of hemorrhagic nephritis and expressing the opinion that the lesions were embolic in nature. In none of his cases, however, was he able to demonstrate bacteria in the affected glomeruli. The reason that he took this view as to the embolic nature of the process was because in one of the larger arteries in one of his sections, there was an embolus which completely occluded the lumen and which contained large numbers of streptocci.

The reason that the lesion has been overlooked is probably because few people had the opportunity of studying a large series of cases. This work has only been possible because of the extensive collection Dr. Libman has made during the past few years.

To be clear upon the etiology of this lesion, it is necessary to understand one or two points concerning the cultural characteristics of the coccus which is one of the commonest causes of this disease. On slant serum-agar it forms a very dry growth, and in broth it grows in very dry clumps which are difficult to break, even by shaking. On the vegetations it similarly grows in small clumps in immense numbers; it is therefore quite possible that the constant stream of blood washing over these vegetations will wash off some of these clumps. This organism has been called by Schottmueller the streptococcus viridans, though more recently Rosenow has produced some evidence which suggested that it is a modified pneumococcus rather than an attenuated streptococcus. Libman and Celler, on the other hand, have shown that this organism possesses characteristics of both the pneumococus and streptococcus, so that the possibility now exists that it may belong in a group intermediate between the two organisms. Until its status is settled, it would be best to adopt Libman's suggestion and speak of the organism in question as the endocarditis coccus of subacute bacterial endocarditis. There is just as much justification for this as there is for calling the diplococcus lanceolatus the pneumococcus.

With one exception the kidneys from the thirty-four cases of subacute bacterial endocardits included in this series were obtained from Dr. Libman's collection. Twenty-seven of these cases were in the bacterial stage, the endocarditis coccus being recovered from twenty-five cases (twenty-two by blood culture during life and three by cultural and miscoscopic examination of the vegetations). In one case the B. influenza was obtained in blood cultures, in another the gonococcus. For this last case I am indebted to Dr. Asch, of the German Hospital.

Glomerular Lesions: The salient features of the pathological picture are, firstly, the involvement of one or more loops of a variable number of glomeruli; secondly, the absence of any visible disease in uninvolved glomeruli, and in the uninvolved portions of affected glomeruli; and thirdly, the association in most of the bacterial cases of all the various stages of the lesion in any one microscopical section.

The very earliest stage of the lesions consists in a swelling of the glomerular epithelium of one or more loops. The swollen cells very soon fuse into a solid mass consisting of a finely granular structureless material in which a few nuclei may still be visible. This granular mass may affect loops at the periphery or in the center of the glomerulus. With hematoxylin it usually takes a deep-blue stain which renders it conspicuous; with Van Gieson's stain it is colored a reddish-brown, or golden-brown, contrasting sharply with loops of other glomeruli which show a later stage. If the process affects loops at the periphery of the Malpighian tuft, the epithelium of the visceral layer of Bowman's capsule undergoes swelling, often some proliferation, and usually desquamation into the capsular space. When the mass with its overlying epithelium comes into contact with the parietal layer of Bowman's capsule, the latter then also may take a share in the proliferation and desquamation.

Eventually this proliferated and desquamated epithelium, which seldom is very extensive, undergoes necrosis as did the previously swollen epithelium of the involved loop of the glomerulus. Then the entire disintegrating mass fuses with the Bowman's capsule and often is seen to become somewhat separated from the remainder of the glomerulus and to become flattened out over the Bowman's capsule in crescentic fashion.

In many pictures like the latter, the finely granular cellular material is seen to be traversed by a very delicate pink staining network. The adjacent interstitial tissue by this time usually shows evidences of some proliferation and is often the site of a small collection of round cells. Fibroblasts may occasionally be observed which are invading the amorphous debris from the connective tissue, and are actively taking part in the production of this fibrillar network. In the same microscopical section, loops of other glomeruli can be seen which are in a still later stage of the process. Here the fibrillar network has thickened to such an extent that it has entirely replaced the necrotic material (except for a few epithelial nuclei), the mass now consisting of dense fibrous tissue. With the single hematoxylin stain this appears as a characteristic wedge of hyaline tissue containing a few nuclei.

Simultaneous with the replacement of the cellular debris by this connective tissue network, there occurs an active growth of the epithelial cells of the adjacent intact portions of the parietal layer of Bowman's capsule. They advance over the inner aspect of the necrotic mass which by this time has usually separated somewhat from the rest of the glomerulus. The result eventually seen represents the healed stage of the lesion; a hyaline mass having roughly the shape of a truncated pyramid, its base fused with the adjacent interstitial tissue, its mesial aspect adherent to the remainder of the glomerulus, its sides clothed by a reflection of the adjacent epithelium of Bowman's capsule.

The portion of the glomerulus involved may be very much larger than here described; it may be a large segment or even the entire Malpighian tuft. In such a case the entire Malpighian body may become converted into a hyaline fibrous body in the peripheral portion, of which the fibrillar tissue may show a tendency toward a crescentic arrangement.

The proportionate number of glomeruli involved varied from 2 to 75 per cent. The average of all the cases studied was 26 per cent. In only two cases among the twenty-five due to the endocarditis coccus, were no glomerular lesions discoverable, although in one case seven and in the other nine blocks taken from various parts of the kidney were examined. Both cases, as far as could be determined, were of very brief duration, though whether this or other factors were the reason for the absence of the lesions, could not be ascertained. In one case due to the B. influenza and one due to the gonococcus, no glomerular lesions were found.

Two other cases among the twenty-five due to the endocarditis coccus, showed a severe disease of the glomeruli, but the pathological picture resembled that of a glomerulo-nephritis. There are reasons, however, for considering the possiblity that the lesions in these cases were also of embolic nature. For the present if we exclude these two cases and the two in which no glomerular lesions were found, twenty-one of the twenty-five cases of subacute bacterial endocarditis due to the endocarditis coccus showed the typical pathological picture in microscopical sections of the kidneys.

In these sections all stages of the glomerular process was usually visible. The early lesions were exclusively present in two cases, the healed in one. In some of the remainder the early stages predominated, in others the late or healed stage.

In the collection which he has exhibited this evening, Dr. Libman has seven hearts which he has for some time considered as typical of the abacterial healing or healed stage of subacute bacterial endocarditis. His opinion was based upon the clinical course of the disease in these individuals, the character of the vegetations and their site. This view received substantial confirmation by the finding of the healed stage of the glomerular lesions in the kidney in six of the seven cases. In the seventh case the glomeruli showed a very marked hypertrophy and a hyaline thickening of the capillary walls in all the Malpighian tufts. Microscopically the kidney presented the typical picture of a secondary contracted kidney. The glomerular change closely resembled that described by Loehlein in secondary contracted kidneys as an antecedent of acute glomerulo-nephritis.

Conclusions.

1. In most cases of subacute bacterial endocarditis, due to the endocarditis coccus, a typical pathological picture is present.
2. In two examples of this disease caused by other organisms, the glomeruli appeared normal.
3. In a group of cases having vegetations which are typical of those in the active stage of subacute bacterial endocarditis, except that they are abacterial and healed, the healed stage of this distinctive glomerular lesion is present.

4. These cases therefore are most probably examples of subacute bacterial endocarditis due originally to the endocarditis coccus, but in which the endocardial vegetations have become abacterial and are healing or healed.

The complete results of the preceding study will later be published in the *Journal of Experimental Medicine.* Details of the work have been omitted as much as possible in this evening's presentation and the conclusions presented as briefly as possible.

For the lantern demonstration, I have to thank Dr. Mandelbaum, who very kindly made the execllent negatives from which the lantern slides were copied. I am indebted to Dr. Libman both for the pathological material with which the study was made and for much helpful advice during its course.

Discussion.

Dr. Libman: Dr. Baehr has inadvertently omitted one of the most important matters in the whole discussion, and that is his extensive studies on the kidney lesions in acute bacterial endocarditis. As he wil tell you, in acute bacterial endocarditis he has never found glomerular lesions such as are found in cases of infection by the attenuated cocci. This means that this kidney lesion is practically pathognomonic of the infection by the endocarditis cocci.

As stated above, the gonococcus case was really not a subacute case. It was only included because the lesions in the heart were similar, and I therefore thought it would be of interest to see whether Dr. Baehr would find lesions in the kidneys similar to those found in subacute bacterial endocarditis.

Dr. Baehr and I will later report on the question of whether the number of lesions in the glomeruli have any relationship to the number of bacteria in the blood. As you have heard, there were two cases with positive bacteriological findings post-mortem, in which no glomerular lesions were found. In one of these cases there were hardly any bacteria in the blood, and in the other case, although five blood cultures were made, they were all negative.

As regards the symptoms which are due to the renal lesions in these cases, they are of great interest clinically. Some of the patients have erythrocytes in the urine; some have marked hematuria; some present the clinical picture of nephritis. Sometimes renal and vesical symptoms are so marked that cases have been diagnosed as being instances of tuberculosis of the kidney or of calculus disease or of pyelitis, and I know of one instance in which the kidney in such a case was removed because it was supposed that the patient was suffering from severe pyelonephritis.

DR. BAEHR: My omission to mention the examination of the kidney glomeruli in the cases of acute-bacterial endocarditis was unintentional. Fifty-four cases of acute endocarditis were studied, the majority of which were of bacterial origin and in none was a single glomerulus found which could be identified as in any respect similar to the typical condition in this disease.

When in acute endocarditis bacterial emboli do occur in glomeruli, they produce a suppurative lesion there. The endocarditis coccus has absolutely no chemotactic action, and therefore the lesions in the kidneys are non-suppurative and they assume this typical appearance.

DEMONSTRATION OF OX-HEARTS SHOWING INJECTION OF THE CONDUCTION SYSTEM.

ALFRED E. COHN

(From the Hospital of the Rockefeller Institute for Medical Research.)

Several ox-hearts were shown. Black India ink was injected into the left division of the auriculo-ventricular bundle. Injection below the undefended space was occasionally successful. Usually the spaces through which the India ink passed were difficult to meet with in this location. It was found easy to insert the small needle into one of the spaces about the ramifications of the apex of the ventricle, where their situation is clearly visible. When neecssary, several such places were sought for, and the injection of the whole system completed. A demonstration of the nature of the arborization of the system is satisfactory only when the injection of the ink takes place before the left division has divided, at the site already mentioned. In the hearts shown both methods had been employed. India ink was used as the injection fluid because it, unlike a number of dyes which had been employed, did not spread into a diffuse stain.

The ink flows through channels which follow the course which Aschoff and Tawara have described as that of the A-V system. When the injected specimen is examined, the left branch appears as an undivided stem, under the endocardium of the left ventricle, a short distance below the aortic ring emerging just below the subaortic muscle. It divdes in two portions which pass toward the posterior and anterior papillary muscles and from them to the venous and arterial bases of the ventricle. The apex and the portion of the ventricle lying between the papillary muscles may be supplied by branches arising separately from the left division. It is quite clear in the light of these preparations that an impulse conveyed over this system must arrive first at the region of the papillary muscles and later at the base. This distribution of the system coincides with the conception that the papillary muscles of the heart contract before the other portions.

The spaces through which the injection fluid passes is not quite clear. The bursa-like spaces described by Curran may be the ones traversed. The distribution excludes the arterial, venous, or lymphatic systems from being channels employed. About the larger branches a single space only is injected. The method of injection proves the continuity of the whole system.

Discussion.

Dr. B. S. Oppenheimer: After hearing of the method through Dr. MacCallum, I injected a few hearts of ungulates with India ink diluted with water, but the injections were not so complete as Dr. Cohn's. A microscopic section of the ventricular wall at a point distant from the site of injection, showed that the spaces around the Purkinje fibers only had been injected. The India ink had also penetrated between the individual Purkinje fibers to a certain extent, outlining them.

FALSE GIGANTISM, MAINLY AFFECTING THE BONES, COMPLICATED BY TRAUMATIC OSTOSES.

JOHN C. A. GERSTER, M.D.

This eleven-year-old boy has no positive facts in his history up to three months ago, when he fell from a wagon, striking his right leg. A swelling promptly appeared at the site of the injury and has persisted there ever since. Two months after the accident, the boy's parents brought him to the University and Bellevue Hospital Medical School's Clinic, asking why it was that the injured leg had grown larger, and why it was that the foot on that side required a shoe two sizes larger than the one of the other side. At the time of application to the clinic there was no pain, fever, loss of weight, or function. There was a limp, due to unequal length of the limbs.

Examination showed the right lower extremity longer than the left, the thighs, however, of equal length, but the right leg one and one-quarter inches longer than the left. The right foot was larger in all dimensions than the left. Two hard, smooth, oval, bony protuberances were felt, immovably attached to the middle third of the tibia. They were absolutely painless. Function of the leg was perfect. The rest of the physical examination revealed nothing of special interest.

X-ray findings: The right tibia and fibula are 1¼ inches longer than the left. There are two subperiosteal bony tumors of the tibia, one the size of a pigeon's egg, the other slightly smaller. The shaft is apparently healthy. The right fibula shows an irregular, diffuse, periosteal thickening as compared to the opposite side. I should like to call attention to certain lines which appear in X-ray plates of long bones in children. These lines lie parallel to the epiphyseal lines and at irregular distances one from the other, but, if the bones of both sides are compared it will be seen that the position of the lines is symmetrical. It may be possible that these lines show periods when growth was arrested and a more intense local bony deposit occurred.

As just said, in normal individuals these lines are symmetrically placed; in this boy's tibiae *the lines on the affected side (although approximately symmetrical) are further apart than on the opposite side.* I take this to indicate that the affected bones have been steadily outstripping their opposite companions ever since very early life.

X-ray plates of the feet show that the entire skeleton of the right foot is larger than that of the left, and measurement of the right os calcis and astragelus show them larger in all dimensions than those of the opposite side. In short, the bony skeleton of the right lower limb, from the knee down, is distinctly larger than that of the left side.

X-ray of the skull shows no enlargement of the pituitary fossa.

Blood examination revealed a slight secondary anaemia. Three Wasserman and one Noguchi reactions were made, all with negative results.

A specimen for microscopical examination was removed; this consisted in a piece from the larger of the two bony masses on the tibia, with some of the adjacent soft tissue.

The report was as follows:

"Microscopical examination of the bone reveals some sclerosis of the cancellous spaces. Microscopical examination of the soft tissues removed from the immediate vicinity of the bone reveals a quantity of poorly nourished fibrous tissue in which are a number of empty vascular spaces apparently of lymphatic nature. There is nothing in the histology to indicate the presence of syphilis or of a new growth.

"SYMMERS, Pathologist."

These tumors seem to me to have been subperiosteal effusions of blood at the time of injury which subsequently became organized into bony tissue—traumatic ostoses.

In short, there is a hypertrophy of part of the bony skeleton (from the right knee down), complicated by the presence of two traumatic ostoses.

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DR. W. G. MACCALLUM, *President.*

THE LESIONS FROM TWO CASES OF BRADYCARDIA ASSOCIATED WITH AURICULAR FIBRILLATION.

ALFRED E. COHN, M.D.

(From the Hospital of the Rockefeller Institute for Medical Research.)

The cases from which the lesions were shown were reported clinically by Dr. James Mackenzie. Dr. Thomas Lewis has also reported the first one.

Lantern slides of the sino-auricular node of the first case at various levels were shown. The node is almost entirely replaced, especially at its lower portion, by connective tissue. The vessel to the node is apparently normal. Sections of the auriculo-ventricular bundle show an old sclerotic lesion of the main stem shortly after the origin of the bundle, causing a complete transverse lesion. The diagnosis of auricular fibrillation and heart-block had been made on the ground that the ventricular rhythm was regular in the presence of auricular fibrillation. The presence of auricular fibrillation was established by means of electrocardiograms.

Sections of the sino-auricular node of the second case showed a very slight degree of fibrosis. A few small haemorrhages (probably ante-mortem) and one area of round cell infiltration were seen. The auriculo-ventricular bundle in this case was not interrupted.

The absence of the A-wave from the jugular pulse, together with complete ventricular irregularity, made it likely even without electric curves, that the auricles in this case, too, were fibrillating. It was supposed that the A-V bundle was capable of conducting impulses. There were periods when the bradycardia gave place to a relative tachycardia, but the rhythm was always irregular.

The two cases are shown together to bring out the fact that accurate clinical diagnosis in these complicated conditions can be made with certainty. The fact that there was an extensive lesion of the node in one case and a relatively slight lesion in the other renders it unlikely that these lesions are responsible for auricular fibrillation. The transverse lesion of the node in one case and a relatively slight lesion in the other renders it unlikely that these lesions are responsible for auricular fibrillation. The transverse lesion of the A-V bundle in the first case determined the regular rhythm; while the intact bundle in the second made a complete ventricular irregularity possible.

The etiological factor in the first case was syphilis. The patient was also a heavy smoker and drinker. The second case was one of arterio-sclerosis. The patient had been a heavy worker and smoker.

Discussion.

DR. MACCALLUM asked Dr. Cohn if he had any idea of the etiological factors in this condition.

DR. COHN said that the first patient was a syphilitic; he had a number of syphilitic lesions, had had malaria, had a marked degree of arterio-sclerosis. Dr. Cohn thought that all these factors would explain this condition.

HODGKIN'S DISEASE INVOLVING THE UTERUS.

W. E. D. JESSUP, M.D.

This case is reported chiefly because of the unusual involvement of the uterus.

Clinical History: Mrs. W., admitted to New York Skin and Cancer Hospital March 17, 1911. Service of Dr. W. S. Bainbridge. Age 43 years. Birthplace Russia. Family history negative. Does not use alcohol. Has had ten children, last four weeks old. One miscarriage.

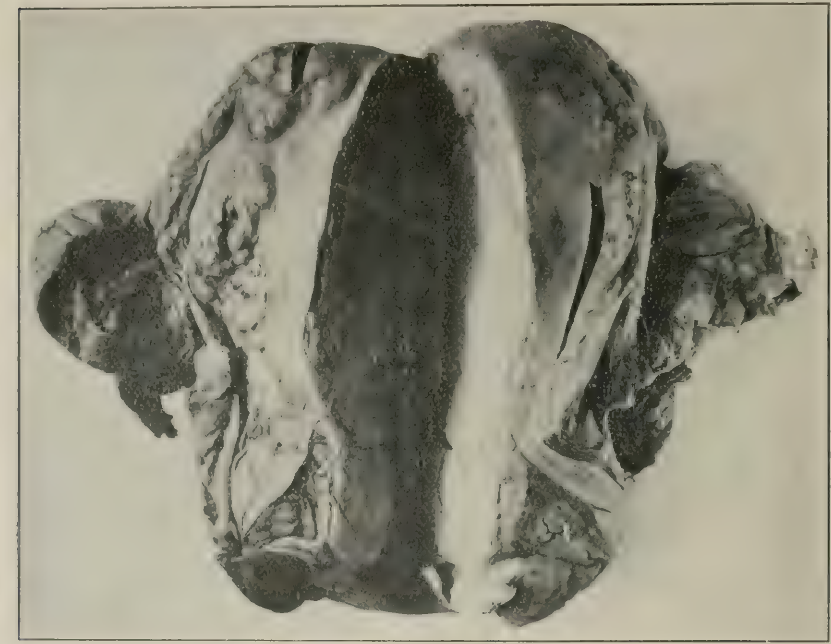
Previous Diseases: Chronic rheumatic manifestation during past year.

Present Illness began November, 1910, with enlargement of glands of both axillae. Two weeks later glands of right groin enlarged. Then glands of neck, and finally general enlargement of external glands to size of pea or larger.

Physical Examination: Poorly nourished, heart and lungs negative. Glands of neck, axillae and groins enlarged. Neck and breasts greatly swollen and skin over this area tense.

Vaginal examination showed enlarged uterus, and clinical diagnosis of sarcoma of uterus was made with metastases in the lymph nodes. Patient was under observation for three months. Axillary and inguinal nodes were excised for examination. Inguinal nodes, removed in March, showed necrosis. A month later axillary nodes showed typical tubercle tissue with giant cells (some of these giant cells later showed tubercle bacilli). The great superficial swelling of the upper part of the body was accompanied by itching. Thickening and infection of the skin resulted from the patient's scratching. Sections of this thickened skin showed inflammatory changes, but nothing on which to base a diagnosis of new growth or Hodgkin's.[1]

During her stay in the hospital patient suffered from pain in the neck and arms, which continued much swollen. There was rapid pulse and dyspnoea and periods of marked restlessness, especially at night. The temperature remained normal except for an occasional short rise. Repeated blood examinations showed an increase of polynuclears, the range being 85 to 93 per cent. There was no increase of eosinophiles. Death appeared to be the result of exhaustion.



Uterus invaded throughout by Hodgkin's disease. Tubes and one ovary also invaded.

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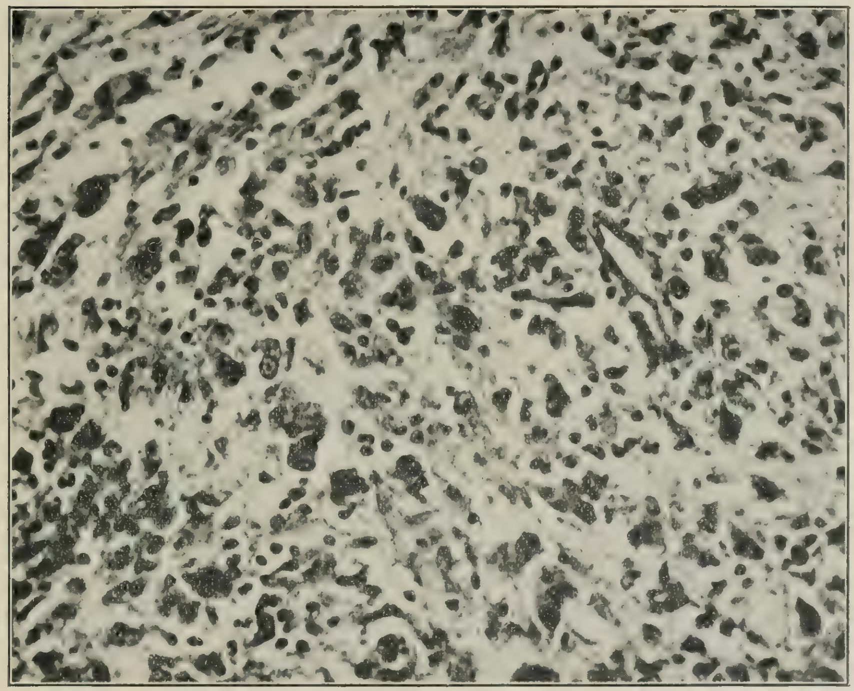
[1] Re-examination of some of these nodes in the light of subsequent diagnosis shows areas suggesting Hodgkins' disease.

Autopsy, by Dr. R. F. Barger, June 25. 1911. Female of about 40; emaciated. Extensive swelling of neck, more so on right side. Rigor mortis not developed. Both axillae and breasts infiltrated with hard nodules; nodules also in groins. Entire body covered with an eruption of spots the size of millet seeds, some crusted, some show complete healing.



Uterine wall near mucosa showing giant cells and endotheloid cells. (x 400)

Thorax: Mediastinal glands enlarged. Left lung collapsed; left pleural cavity filled with bloody fluid. Right lung adherent.

Heart: Normal.

Spleen: Normal size; shows small white nodules.

Kidneys and Pancreas: Normal.

Liver: Congested.

Gall Bladder: Normal.

Iliac lymph nodes enlarged, ranging in size from 1/3 cm.

Mesenteric nodes uniformly enlarged.

Stomach: Normal.

Uterus: Measures 12 cm. in length and is 9 x 6 cm. at fundus. Surface nodular. Entire wall infiltrated with growth of dense fibrous tissue, which has caused apparent destruction of all the muscularis.

Tubes: Show similar nodular thickening at uterine end.

Ovaries: Normal size and fibrous. In one there is an area of growth similar to that in uterus.

Microscopical Examination.

Sections of different parts of the uterus show growth of epithelial cells, small round cells, with scattered giant cells. Portions are densely fibrous in character. The structure of the mucosa is almost entirely lost, only a few scattered glands remaining. One ovary, the Fallopian tubes, the mesenteric, iliac and bronchial lymph nodes, spleen and breasts show similar growths; also the deeper layers of the skin of neck. The smaller nodules, especially those in the spleen, show the large type of cells, with mitoses and very little of the dense fibrous changes seen especially in the uterus and some of the lymph nodes.

Diagnosis.

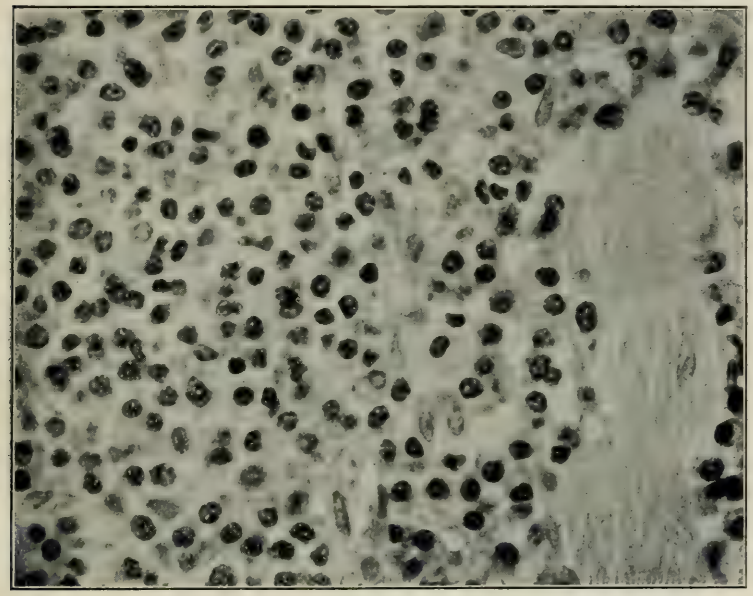
Hodgkin's disease, involving the uterus with tuberculosis of some of the superficial lymph nodes.

PLASMA CELL TUMOR OF THE TONGUE.

For permission to show slides from this case I am indebted to Dr. E. M. Foote, in whose service at the New York Skin and Cancer Hospital the tumor was removed. Some members of this Society have already had an opportunity of examining the tumor, and the patient was shown last March at a meeting of the New York Surgical Society.

Mr. P., 45 years of age. Family history negative. Venereal history negative. Habits: moderate use of tobacco up to four years ago. Typhoid when a child. Muscular rheumatism four years ago.

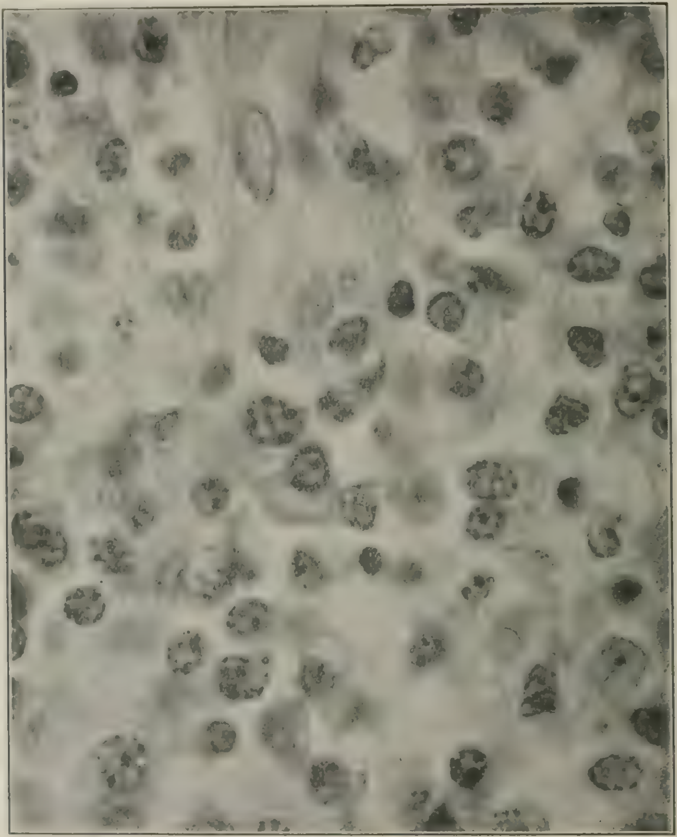
In 1901 a rectal abscess was incised and drained with three subsequent operations. Final healing four years ago, and then mouth became tender with swelling of lips, cheeks, and gums. In December, 1909, portions of the lips and cheeks were cut away. In July, 1910, tongue was cauterized twice by Dr. Mayo of Rochester. On admission to hospital, November, 1910, patient complained of enlargement and soreness of tongue.



Plasma cells and muscle fibre, high power.

The Wassermann reaction was negative.

Physical Examination: Heart, lungs, and abdomen negative. Tongue showed on dorsum a swelling 1½ cm. across and along left border a cicatrix 1 cm. wide. These portions were excised and submitted for examination. After patient left hospital, the tongue continued to enlarge and a second operation, removing tip of tongue, was performed. Subsequently patient developed a cough, and tubercle bacilli were found in sputum. The growth of the tongue appeared to be arrested after the second operation.



Plasma cells (x 1000)

Pathological Examination of Tongue: Macroscopical Examination: (a) Wedge from dorsum of tongue, 3.5 x 2 cm. and 1 cm. thick. Surface has warty appearance. On section, tissue below epithelium is firm, pale, and homogeneous in appearance.

(b) Wedge from side of tongue, site of former operation, 5.3 x 1.8 cm. and 1 cm. thick. Center of surface occupied by cicatrix 1 cm. broad. On section, tisue appears like that from dorsum.

Microscopical Examination.

Sections from different parts of both specimens show same character of growth. Beneath the surface epithelium, and extending down and invading the muscular layer, is a growth of large cells with a large oval or round nucleus with abundant chromatin. The growth is diffuse and there is no grouping of the cells in nests, nor do they seem intimately connected with the connective tissue framework. Where the muscle is invaded there is atrophy of the fibers. Levaditi stain for spirochaetae is negative, as is also stain for tubercle bacilli. In the region of the scar there is inflammatory infiltration. Examination of portion of growth from tip of tongue removed at second operation showed similar growth of cells of the plasma-cell type with more congestion and inflammatory infiltration.

Diagnosis.

It seems possible to rule out sarcoma and syphilis and in the absence of giant cells, tubercle tissue and tubercle bacilli diagnosis of tuberculosis does not seem justified. The growth appears to belong to the group of plasma cell tumors which have been described by several observers, and to which the name "plasmoma" or "plasmocytoma" might be applied.

The literature shows reports of a few tumors composed largely of plasma cells; some arising in bone marrow with the characteristics of a malignant tumor, others of apparently benign character. Of the former type two may be cited, published by Hoffman (*Ziegler's Beiträge*, Bd. 35, 1904, p. 317) and Wright (*Jour. Boston Soc. Med. Sci.*, 1900, p. 195). The tumors originated in the marrow and were multiple, with metastases involving the bone in various parts of the body. A somewhat different type is described by Maresch (*Verhandlungen d. deutsch. path.*

Gesselschaft. 13. Tagung. Leipzig. 1909) in a tumor that was removed from the neck which proved to be largely made up of plasma cells. After the death of the patient similar nodules were found in the liver, spleen, and bone marrow.

In the second group belong the cases of Schridde (*Zentralblatt f. all. Path., u. path. Anat.*, Bd. 16, 1905, p. 433), and Bolt (*Frank. Zeits. f. Path.*, Bd. 1, 1907, p. 172). Schridde's case was from the nose and was first thought to be a rhinoscleroma, but both the bacilli and Mikulicz cells were absent. Bolt's case came from the naso-pharynx, and was a tumor about 1½ cm. in diameter. The tumor did not recur after excision. The case of Werdt (*Frank. Zeits. f. Path*, vi, 1911, p. 180) was a movable tumor of the naso-pharynx, pushing forward the uvula, and about 2 cm. in diameter. The mass had an uneven lobular surface and was of a bluish-red color. No recurrence was noted some months after operation. Microscopically it was composed of closely packed plasma cells, with a scanty fibrillar stroma. Hedinger (*Frank. Zeits. f. Path.*, vii, 1911, p. 343) describes a tumor measuring 8 x 20 mm., arising in connection with long standing adenocarcinoma of the sweat glands of the scalp. The tumor was formed almost entirely of hydropic plasma cells. At first glance it resembled a large-celled sarcoma with transition areas into granulation tissue; but on staining the cells by special methods they showed the morphology of true plasma cells lying in a meshwork of delicate connective tissue. The regionary lymph nodes were invaded by the adenocarcinoma, but no metastases had been formed by the plasma cells. The mass must be considered not as a true tumor but as an inflammatory new growth, there having been a recurring inflammation about the carcinoma of the scalp.

This tumor of the tongue would appear to belong to the second group of benign plasma cell tumors.

Discussion.

Dr. Levin: I should like to ask Dr. Jessup from what part of the tongue the piece of which the photograph is shown here was taken. If I understand the case correctly, there are a number of ulcerations around the tongue, and the tongue is enlarged; but what is not clear to me is where that part is situated which served for the microsocpical study. If one should judge from the appearance of the tongue, the question arises whether the condition is not an inflammatory one. I have recently seen a tongue very similar to the one presented here, which, after a few weeks of treatment with mild antiseptic applications, became normal.

Dr. MacCallum felt that the assumption of Wright and Hoffman and others of the plasma cell nature of the elements of certain tumors which they have described should be received with some hesitation, because plasma cells are in their very nature independent wandering cells, and it would be like speaking of a tumor composed of polymorphonuclear leucocytes. If these are plasma cells, it seems necessary to consider the possible inflammatory nature of the lesion which Dr. Jessup describes.

Dr. Ewing: I should like to ask the doctor if he is satisfied that he can explain the tuberculous infection of the lymph nodes in one portion of the lymphatic system, as a secondary infection.

In regard to the second case, I was much interested to see that case turn up at this time, as I spent a good many hours working and worrying over it; the material was sent to me two or three times. I agree with Dr. Jessup in the main conclusion that he makes that we have to deal with a tumor, or tumor-like process, in which the cellular elements resemble plasma cells, and that is about all that can be said. I fail to find anything in the literature which accords with this condition. When I heard a few weeks ago that tubercle bacilli had been found in this patient's sputum, I felt that that was an additional factor which might explain the condition of the tongue, and I am disappointed to find that Dr. Jessup is not inclined to associate this condition with a tuberculous process in the lung.

I did not at any time believe the process was a true sarcoma, although it came into my hands with a diagnosis of sarcoma from several sources. To me the proces is extremely interesting and quite obscure, and while I agree with the diagnosis in general that Dr. Jessup has given, I do not think the condition has anything to do with the ordinary myeloma.

Dr. Jessup: In reply to Dr. Ewing's question in regard to the glands: These glands, as I said, were examined during the life of the patient on two or three occasions, and the only definite thing found was the tuberculosis. There were some glands which were very fibrous and tough, and looking through them now in the light of the subsequent diagnosis, there are areas from which I think the diagnosis of Hodgkin's could be made. Of course, I assume that the tuberculosis was a secondary development. It was certainly present at the time the patient came to the hospital.

With regard to the question about the part of the tongue from which this photograph section was removed, of the two specimens passed around, the one with the smooth surface was the portion that was operated upon and that central elevation was the portion sectioned for this photograph. Subsequent operation from the tip of the tongue showed a similar condition.

With regard to Dr. MacCallum's question about other cases of Hodgkin's, I have not had time to look through all the literature. I have looked through Kurt Ziegler's recent monograph, and he has reported a number of cases in which he has found Hodgkin's in the ovaries and also in the testicles, but I could find no case involvinig the uterus.

THE VALUE OF ABSORPTION METHODS IN THE WASSERMANN TEST.

MIRIAM P. OLMSTEAD.

(From the Department of Health, Research Laboratory, New York City.)

A series of comparative Wassermann tests has recently been made to determine the value of Rossi's and Wechselmann's methods of absorbing from the serum to be tested for syphilitic antibodies, certain components that interfere with a positive reaction.

Natural anti-sheep amboceptor is frequently present in human serum, so that on the addition of two units of amboceptor in the course of the Wassermann test there is an excess of amboceptor and hemolysis is unduly increased. Rossi[1] has described a method of absorbing the natural amboceptor from the serum previous to the test, thus insuring the balance of the hemolytic system and increasing the delicacy of the reaction of the Bauer modification,[2] which depends for at least part of the hemolytic action on the natural amboceptor content of the serum. As this is an unknown quantity, varying from zero to twenty or more units, there is no certainty of the hemolytic system being in balance, and the accuracy of the reaction cannot be depended upon.

The presence of natural anti-sheep amboceptor in the serum is first determined by incubating for one hour in the water-bath at 37° C. two parts of inactive serum, two units of complement, one part of 5 per cent. sheep cell suspension and twenty-eight parts of physiological salt solution. Hemolysis, partial or complete, indicates the presence of anti-sheep amboceptor, which, according to Rossi, may be removed as follows:

Three parts of inactive serum and one part of washed packed sheep cells are mixed, kept on ice for from twenty to thirty minutes, and then quickly centrifugated. The serum that is drawn off is tested as usual.

Out of eighty-eight sera tested by us for amboceptor, forty-four, or 50 per cent., gave evidence of the presence of natural anti-sheep emboceptor; and these same sera tested after absorption had no hemolytic action on sheep cells, indicating that absorption had taken place.

A comparison of Wassermann tests on absorbed and untreated specimens verifies Rossi's assertion that an excess of amboceptor interferes with a positive reaction in the diagnosis of syphilis. Of forty-seven specimens that gave a negative reaction in the regular Wassermann test, five, 10.6 per cent., were positive after absorption. Two were from undoubtedly specific cases and both of these gave a positive reaction after absorption. Eleven had a past history of syphilis, but no present symptoms: of these one gave a positive reaction after the absorption. Of the twenty-nine cases with a suspicious history, two gave a positive reaction after absorption. Five cases with no luetic history remained negative after absorption. Experience has shown that if the cells used in absorption are not thoroughly packed the serum is so diluted that it reacts no more strongly than in the unmodified test. Our tests give no indication of any danger of false positive reactions through the use of Rossi's method.

Wechselmann[3] called attention to the presence in heated serum of complementoids, which, though they have no hemolytic action, retain haptophore groups, hence are capable of being bound by the antigen-antibody combination and prevent the latter from binding complement, which is thus left free to hemolyse the cells subsequently added.

Noguchi[1] and others have expressed doubt as to the complementoid nature of the serum components thus preventing a positive reaction, but agree that the accuracy of the test is increased by their absorption.

Wechselmann recommends treating all sera to be tested for syphilis with barium sulfate, which has the power of absorbing complementoids and hence increases the binding of complement. The technique of the absorption is as follows:

Nine parts of inactive serum, thirty parts of physiological salt solution and five parts of a 7 per cent. suspension of freshly precipitated barium sulphate are shaken together, incubated for an hour at 37° C. and centrifugated. Of the supernatant fluid, ten times the regular amount for the Wassermann test must be used.

We have treated in this way forty-three specimens that had given a negative reaction in the unmodified Wassermann test, six of which—a percentage of 13.9—gave a positive reaction after absorption. Five specimens from which a history of syphilis could be absolutely excluded were even more clearly negative after treatment with barium sulfate than before. Seven positive sera have been treated with barium sulfate and have not thereby lost any binding power. That barium sulfate itself has no binding power has been controlled in each set of tests by a treated negative serum or by barium sulfate and salt solution alone.

Eight specimens with a suspicious gonorrheal history that had given a negative reaction in the unmodified complement-fixation test for gonorrheal antibodies were treated with barium sulfate, after which two of them reacted positively, suggesting that Wechselmann's absorption method might be of as much value in the serum diagnosis of gonorrhea as of syphilis.

At Dr. McNeil's suggestion a combination of the Rossi and Wechselmann methods was tried, in order to absorb the natural amboceptor as well as the other serum components that interfere with a positive reaction. Sixty-six specimens that had given a negative reaction in the unmodified test were treated first with sheep cells and then with barium sulfate; eighteen of these, 27.2 per cent., were positive after absorption.

Exactly the same percentage was obtained in similar tests for gonorrheal antibodies, three out of eleven negative specimens being made positive by absorption with sheep cells and barium sulfate.

Wolff[5] has emphasized the value of the barium sulfate treatment for the absorption of complement as well as complementoid; and he advises the use of active rather than inactive serum, as heating at 56° C. destroys some antibodies, thus weakening a positive reaction.

We have treated with barium sulfate twenty-eight negative specimens of active serum. Nine of these, 32.1 per cent., gave a positive reaction after absorption. Although this percentage is higher than in the series of tests with inactive serum from which both natural amboceptor and complementoids had been absorbed, the use of active serum does not seem to be advisable. Three specimens from which a history of syphilis[6] could be absolutely excluded gave a positive reaction and in at least one other instance it seemed highly probable that the binding was non-specific.[7] In a number of instances (eleven) one-tenth c.c. of serum bound more strongly than two-tenths. Though this phenomenon has not been constant, it has occurerd so frequently as to render the test unreliable.

Wechselmann, Wolff and others have emphasized the non-suitability of commercial barium sulfate for absorption purposes; but they have not stated how fresh a precipitate should be used We have found a precipitate four weeks old as effective as a perfectly fresh one. Since, however, a suspension is apt to become anticomplementary in three or four weeks it is advisable to use a fresh suspension about every two weeks. A simple method of precipitating barium sulfate is described by Wolff.[1]

Mix fifteen c.c. of 5 per cent. sodium sulfate and 10 c.c. of 5 per cent. barium chloride. Centrifugate after precipitation has taken place, draw off the supernatant fluid and wash the residue, barium sulfate, once in physiological salt solution. After centrifugalization suspend the barium sulfate sediment in 25 c.c. of physiological salt solution, which makes the proper dilution for use in absorption.

Summary: Thus it appears that by absorption methods the number of positve reactions in the Wassermann test for syphilis is increased. The relative value of the Rossi, Wechselmann and Wolff methods of absorption is indicated by the following comparison of the various tests just described:

By the absorption of natural amboceptor by sheep cells 10.6 per cent. of the negative specimens were made positive.

By the treatment of inactive serum with barium sulfate 13.0 per cent. of the negative specimens were made positive.

By the use of both sheep cells and barium sulfate on inactive serum, 27.2 per cent. of the negative specimens were made positive.

By the treatment of active serum with barium sulfate 32.1 per cent. of the negative specimens were made positive.

Wolff's method of treating active serum with barium sulfate gives the highest percentage but is not, according to our experience, reliable.

The combination of Rossi's and Wechselmann's methods gives a high percentage; and so far as may be judged from the results of our few tests, there is no danger of thereby rendering the Wassermann reaction over sensitive. The effect of barium sulfate on sera free from syphilitic and gonorrhoeal antibodies should, however, be tested at length before the use of barium sulfate in the routine serum diagnosis of venereal diseases is recommended.

Rossi's method of absorbing natural amboceptor from the serum to be tested is of practical value and perfectly safe.

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SIGNIFICANCE OF THE GROUP OF "HEMOPHILIC" BACILLI IN CONJUNCTIVITIS, ESPECIALLY IN THAT OF "TRACHOMA."

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During the past year and a half ten workers have been grouped in the Health Department for the purpose of studying trachoma and allied conditions from all standpoints, but especially from that of the public school children of New York City. These workers have been advised and encouraged most helpfully by Dr. Wm. H. Park, Director of Laboratories. The paper tonight is a report of one phase of the work—a part of the bacteriologic study—and it will emphasize only two points.

From the important papers of Dr. Noguchi and Dr. Cohen[1-2] read before this Society in 1910-11, we have had a good opportunity of learning of some of the recent work that has been done on the etiology of trachoma: how certain epithelial cell inclusions, which have been found in large numbers in the acute papillary stages of the disease, are considered by the majority of the many students of this subject to be the cause of trachoma. Noguchi and Cohen believe that these inclusions are an accompanying infection; Wolbach, McKee[3], Addario[4] and a very few others think they are degeneration products of the epithelial cell; while Hertzog[5] and a few others think they are involution forms of the gonococcus.

From time to time in the history of trachoma investigations the claim that the gonococcus is an etiologic factor in trachoma has been urged. In order to find out whether or not the gonococcus had anything to do with the trachomatous eyes of school children, and at the same time to make a more comprehensive bacteriologic study of these eyes and to continue the investigations of the trachoma inclusions started by C. R. Gurley and J. Chase in our laboratory in 1910 this part of the study was planned. An eye clinic was established in the Research Laboratory, with Dr. Wootton, the Department's Ophthalmologist, in charge, assisted by Dr. Von Sholly, Miss Gurley and others of the group.

A history and a minute record of the course of each case has been kept by the folder and card index system. All of the charts and chart holders for the work as well as a certain amount of money for the carfare of those children living at a distance and too poor to pay were presented by the Committee on the Prevention of Blindness of the Sage Foundation. These aids were most helpful to us in getting quickly and satisfactorily into the work.

Following the course for so long a time of such a large series of cases of all types of conjunctivitis by full written records has seldom, if ever, been done before. It has allowed us to make the column of recovering cases seen in Table 1 and to trace a certain number of cases from acute catarrh through a series of attacks to papillary trachoma with typical inclusions. Tables showing the course of the cases will be given in the full report at a later date. We mean to keep track of the cases of trachoma which we have recorded as cured with the exception of mild folliculoses, in order to determine if possible whether subsequent symptoms of trachoma are the result of an exacerbation or a reinfection.

In our clinic after the minute description of the eye condition was recorded, in each new case, and from time to time in some of the older cases, a light curettage of the palpebral conjunctivae was made, then a sterile cotton swab was rubbed over the curetted areas and was placed immediately into a tube of ascitic-broth which was taken at once to the laboratory, where part of it was planted on a series of culture media plates, including glucose-ascitic agar, blood agar and plain alkaline veal agar. All were then placed in the incubator at 36° C., and were examined within 24 hours, and later when necessary.

From one case among the first growth, Miss Wilson found a few gonococcus-like colonies on glucose-ascitic agar and on blood agar. These were fished and were found to be a tiny gram negative bacillus which was strictly hemoglobinophilic. Since then, rabbit blood broth, instead of ascitic-broth has been used for the cultures taken directly from the eye, since this medium is better for the tiny bacillus and equally good for the gonococcus. The blood broth acts as an enriching medium in those instances—and they are not few—where there is no growth on the original plates. After about 24 hours in the incubator the blood broth in practically all the acute papillary trachoma cases (Table I) has shown an abundant growth of the little bacillus, and blood agar plates made at this time from the blood broth culture generally have given many typical colonies. This tiny bacillus in blood broth grows in small and large compact groups which, after Gram, counterstained by fuchsin, appear under the low power as small granular masses taking a brilliant red stain. The individual bacillus does not show so brilliant a stain. Stained by

Giemsa *these small groups of bacilli have morphology and staining characteristics very similar to those of some of the trachoma inclusions.* Our attention was thus early directed to the question of the identity of the two. I shall speak of this a little later.

In looking up the literature on hemoglobinophilic bacilli found in eye diseases (Table II), I was surprised to find that most investigators say that the influenza bacillus is found rather infrequently—with the exception of Müller's series of cases; and that the Koch-Weeks bacillus is found practically only in acute conjunctivitis—*and that it grows better on serum agar than on blood agar.* Müller[6] found in a large percentage of his acute trachoma cases in Egypt a tiny bacillus which he could not differentiate from the influenza bacillus, though he thought it was another species, since there were no cases of influenza about.

In Manila recently Edwards[7] found in a few cases of trachoma a minute Gram-negative bacillus which was a strict hemoglobinophilic. He called it *B. trachus,* and suggested that it might produce the trachoma inclusions.

A few authors—Kamen[8] and others, claim that the Koch-Weeks bacillus is a strict hemoglobinophilic and that the cultural work of those who claim otherwise is open to criticism.

So we had first before us the problem of the relationship of our bacillus to the influenza and the Koch-Weeks bacillus.

After carefully examining a series of clinically typical "pink eye" and getting an abundant, practically pure growth of a bacillus similar in general to the one we were isolating from our papillary trachoma cases, we were forced to the conclusion that those who consider the Koch-Weeks bacillus a strict hemoglobinophilic are correct. The word hemophilic, therefore, in Table II and in the title of this paper should be changed to hemoglobinophilic. Furthermore, in this series of cases of "pink eye" we found that the size of the bacillus in the direct smear of the exudate varied from coccus forms to comparatively long forms, while the pure cultures did not always vary correspondingily, hence we cannot consider the point of size in the direct smear of worth in differentiating Koch-Weeks and the influenza bacillus (see Table II). It was surprising to us to find in the direct smear from several of the cases of "pink eye" so few distinct bacilli, although the culture plates showed an abundant growth. In these smears and in the direct smears from our trachoma and follicular conjunctivitis cases where the tiny bacillus was almost invariably found, no recognizable bacilli were seen within the leucocytes, while we found the groups lying within the cells for the most part scattered and atypical—corresponding frequently to Lindner's[9] extra cellular "initial bodies," found in his cases of trachoma.

It has been stated that trachoma gives no constant bacteriologic findings. In order to get further evidence on this point, that is, to find whether or not the tiny bacillus we were finding so constantly in our cases of papillary trachoma were present in the cases direct from other countries, we are examining at Ellis Island, through the kindness of Dr. Stoner, Chief Medical Officer, and of his assistants, cases of typical and doubtful trachoma in the immigrants. We have already examined 16 cases, in three of which with marked papillary trachoma both hemoglobinophilic bacilli and trachoma inclusions were found. In four border line cases and two follicular conjunctivitis cases only bacilli were found, while in seven recovering cases no bacilli were found, and only a few inclusions in three of these. Thus, so far, these findings correspond with those of our school children.

We have isolated, in all, 128 strains of a hemoglobinophilic bacillus from our series of 213 cases (Table II), and we have as yet not been able to find any distinct differential points between any of them or between our strains and those of the B. influenzae as described by others or as studied by us. Two strains of the B. influenzae kindly sent us by Dr. Wollstein have been studied with our cultures.

It is true that certain of our strains show small peculiarities which seem to be holding through many culture generations, such as greater tendency to thread formation, more marked pleomorphism, large or small size, etc.; but so far we have found no distinct relationship between these characteristics and the clinical picture.

We are compelled, therefore, for the present to group all of these bacilli with the influenza bacillus.

Dr. MacNeal and Dr. Povitzky are studying complement deviation of the group, but so far have encountered little but difficulties.

Miss Mishulow is getting some interesting results with symbiosis studies, but at present they can only be used practically to show some of the difficulties in the way of demonstrating and of isolating the little bacillus. Staphylococci seem to have a decidedly inhibitory action on the growth, especially in blood broth, while certain non-hemolysing streptococci favor the growth slightly, and the xerosis group shows a markedly favorable action. On non-blood media, growth has been obtained only with the xerosis bacillus.

The fact that the staphylococcus inhibits growth may account in part for negative results in some of our apparently recovering cases where staphylococci were in abundance.

I said that early pure cultures show a resemblance to some trachoma inclusions. These early cultures show many forms similar to Lindner's initial bodies and smears taken daily from the same culture and stained by Giemsa show morphologically a similar cycle of development to that described by Prowazek and others, especially by Lindner[10] in 1910, for the famed chlamydozoa of trachoma or the trachoma inclusions. In other words, in the culture of the tiny hemoglobinophilic bacillus we have, morphologically, a culture of the trachoma inclusions. Thus we have, first tiny coccus-like or short bacillar bodies taking a clear blue stain, and later the appearance of very tiny metachromatic granules within these blue bodies, then the gradual disappearance of the blue bodies leaving a mass of metachromatic granules. I have placed under the microscopes some initial inclusions and a more developed included form from a case of papillary trachoma, also smears of a culture from the same case made after 2, 3 and 5 days' growth on blood agar, and you can readily see for yourselves the striking resemblance between the two, a resemblance still more striking when many smears and cultures are examined.

That the epithelial cells of the conjunctiva may take up bacteria is a well-known fact, but nobody before has, to my knowledge, followed the cycle of development of the bacteria within the cells, and no one has recognized the possibility of any of the groups of hemoglobinophilic bacilli found by us so frequently in trachoma having the power to grow in the epithelial cells, except Edwards, who merely suggested that the bacilli which he found might produce the trachoma inclusions.

In most cases of blenorrhoea, gonococci are found in the conjunctival epithelial cells, and since these organisms in pure cultures pass through a cycle of development somewhat similar to that of the hemoglobinophilic bacillus, that is, the production ultimately of masses of metachromatic granules in the cultures, with the gradual disappearance of the blue-staining organisms, there is reason to suppose that they, too, may form inclusions, especially in certain cases, although this is a subject which needs much further study in connection with a bacteriologic study of gonorrhoic and non-gonorrhoic opthalmia neanotorum.

In none of our school children cases so far have we found gonococci. While the two facts which we wish to emphasize in this paper, namely, first, the finding of our tiny bacillus so uniformly in our cases of papillary trachoma, where we have found, too, the trachoma inclusions, and second, their morphologic similarity, lead us to conclude that bacillus and inclusions are probably identical in papillary trachoma, and hence that the bacillus is probably the cause of the disease.

The hypothesis that one or more of the group of hemoglobinophilic bacilli is the cause of trachoma explains many other hitherto unexplanable phenomena of this disease, (1) its regular onset; (2) its insidious course; (3) its variable contagiousness, with its exacerbation of secretion; (4) the continued presence of trachoma in certain districts where helping causes are present, etc. Of course, suitable monkey inoculations would in all probability be all that is necessary for proof or disproof. It is, to say the least, a very good working hypothesis. For it means practically that all cases of secreting conjunctivitis, however mild, should be looked after until all secretion has ceased. With organisms of this type which presumably may lose their virulence quickly, sufficient oversight of cases gives great hope of getting rid of dangerous carriers. On the strength of these results we are strongly advocating and trying to get established special mixed classes for the school children who are now being sent to school with very slight secretions while receiving treatment at clinics. The Board of Education has the plans under consideration. We are also advocating more minute home inspection and instruction, and we are hoping for help in this part of the work from organizations whose work lies in these directions.

To lessen the disease among our immigrants, our immediate hope is the establishment by the ship companies of more prophylactic measures on board ship. Wtih arrangements for the isolating of *all* secreting eye cases, and the helping to keep *all* eyes clean by boric acid solutions, etc., the Immigration Bureau at Ellis Island would in all probability not need to deport, as they do now from time to time, a whole group of cases of acute papillary trachoma.

With these measures established, if our hypothesis is correct, we can hope in a reasonable time to have trachoma under control, if not practically stamped out.

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Table I.

Showing Relative Occurrence of Hemoglobinophilic Bacilli and Trachoma Inclusions, in author's series of cases.

"Trachoma"									Acute Conjunctivitis			Follicular Conjunctivitis			Folliculosis		
Acute			Old			Recovering											
Number of Cases	Bacilli	Trachoma Inclusions	Number of Cases	Bacilli	Trachoma Inclusions	Number of Cases	Bacilli	Trachoma Inclusions	Number of Cases	Bacilli	Trachoma Inclusions	Number of Cases	Bacilli	Trachoma Inclusions	Number of Cases	Bacilli	Trachoma Inclusions
41	+	+	9	—	—	23	—	—	4	—	—	9	—	—	11	—	—
5	+	—	6	+	—	7	+	—	12	+	—	15	+	—			
1	—	+	9	—	+	14	—	+									

Table II.

Showing several Points in Group of "Hemophilic" Bacilli as noted in Published Reports.

Names	Where Found							Differential Points		
	Human Beings						Lower Animals.			
	Eye	Ear	Respiratory Tract	Meninges	Gen. Urin Tract	Other Locations	Gen. Urin	Size	Hemoglobin	Pathogenicity Lower An'mls
B. influenzæ (Pfeiffer)	+	+	+	+	+	+		Short	+	+ —
B. of Müller	+							Short		
B. of Koch-Weeks	+		+					Longer	— +	—
B trachus (Edwards)	+							Short	+	
B. of Davis					+			Short	+	—
B. hemoglobinophilis, canis (Friedberger)							+	Short	+	—
Hemoglobinophilic bacilli in author's series of cases	+		+		+			Short Longer	+	+ —
Trachoma Inclusions	+				+			Small Longer		+ —

TABLE III.

Showing Frequency of Hemoglobinophilic Bacilli in Author's Series of Cases.

Diagnosis		Number of Cases Examined	Number of Cases Showing Bacilli
Acute Conjunctivitis ("Pink Eye," etc)		47	38
"Trachoma"	Acute Papillary Conjunctivitis	47	46
	Old and Recovering Cases	68	13
Follicular Conjunctivitis		40	31
Folliculosis		11	0
Total		213	128

Discussion.

DR. WOOTON: Dr. Williams' classification, approached from the clinical standpoint, amounts to about this: Those cases that she has classified as papillary conjunctivitis exhibit hypertrophied conjunctivæ, the blood vessels are either partially or completely obscured, and if follicles be discernible the interstices between them are obliterated by the hypertrophy.

In her cases of folliculosis there is merely a formation of follicles without hypertrophy, and her cases of follicular conjunctivitis are clinically folliculosis with secretion added. The cicatricial forms of trachoma are too well known to require description.

Now, in regard to the cases of papillary conjunctivitis we have followed a good many of them at the Research Laboratory, occurring in school children, and it has been a question whether they ever go on to cicatrization and pannus. I have, however, seen pannus follow in two cases. In these cases of papillary conjunctivitis the trachoma bodies of Halberstaedter and Prowazek are found practically without exception, and we may consider them from the point of view of one or the other of two theories.

The theory advanced by Cohen and Noguchi is that the trachoma bodies do not necessarily imply trachoma at all, but that they are characteristic of an independent conjunctival infection which may become ingrafted on other conditions. If, on the other hand, we start with Dr. Williams' hypothesis, that these various stages of conjunctival affection are different stages of the same disease, caused by repeated infections, possibly with a hemoglobinophilic bacillus which in a certain stage of its development is related to the trachoma bodies, then we must regard these cases of papillary conjunctivitis in children as one of the stages of trachoma.

Dr. Williams' theory certainly explains the tendency of the disease to extend itself in overcrowded communities. Trachoma is not a disease that belongs to any country or to any race, but sometimes to different races in different countries, and always under such circumstances does it afflict those who are overcrowded and live under conditions which render repeated infections likely to take place.

The cases that I have studied at the Research Laboratory have mostly occurred in children. In the adult cases the character of the papillary hypertrophy is in my opinion somewhat different.

RECENT VIEWS ON INFLAMMATION OF THE ENDOMETRIUM AND "ENDOMETRITIS."

ROBERT T. FRANK.

Formerly every seeming glandular increase was classified as "hypertrophic or hyperplastic glandular endometritis." No correspondence between clinical types and pathological findings could be drawn. In the last few years our knowledge has been greatly increased by new investigations. Unfortunatly these newer findings have been scarcely heeded in the United States.

Hitschmann and Adler in 1908 reported upon the changes which occur in the normal human endometrium under the influence of the ovary. As described by them, a regular monthly cycle, divisible into four phases, could be observed. (1) The *premenstrual stage* (stage of secretion) is characterized by marked glandular activity, increase in size of glands, enlargement of cells distended with secretion, pseudopapillary formations, and decidual stroma changes. (2) *Menstruation* is accompanied by rapid deturgescence, with extrusion of red blood cells into the stroma and later into the uterine lumen. The gland cells pour out their secretion and rapidly assume simple shapes. (3) The *postmenstrual stage* (stage of rest) corresponds to what formerly was called normal endometrium—simple glands, spindle and round celled stroma. (4) The *Interval* is marked by growth of all constituents. The glands enlarge, saw-tooth forms, high columnar epithelium, mitoses; the stroma shows the beginning of decidual changes and mitotic changes.

Hitschmann and Adler considered the hitherto described glandular forms of "endometritis" as normal premenstrual changes. They limited the term "endometritis" to interstitial forms and considered as sole criteria of inflammation the presence of plasma cells.

The large number of subsequent investigators accept the findings of Hitschmann and Adler with great reserve. All acknowledge that cyclical changes take place, but the consensus of opinion is that no rigid schema can be drawn up. Furthermore, future investigation has shown that, though the presence of plasma cells is a sure sign of inflammation, these cells disappear long before inflammation ceases, and that, therefore, the absence of plasma cells is no guarantee that no inflammation exists.

The main question now resolves itself into whether we can recognize the usual signs of inflammation—exudative, vascular and stroma changes—in spite of the constant cyclical variations, which tend to mask them, and whether true inflammatory affections of the endometrium influence the clinical course. Authors who have attempted to furnish descriptions of pathognomonic changes (for instance Albrecht and Logothetopulos) offer no criteria which are convincing. Others, who interpret exaggerated or irregular phases, as due to disturbed ovarian function, are able to correlate the morphological and clinical data to better advantage (Beuttner).

From the evidence at hand it appears certain that minor and moderate changes in the composition of the endometrium—hitherto classified as "endometritis"—are accounted for by cyclical changes; that plasma cells, when present, are a sure sign of inflammation, but that their absence does not make certain the absence of inflammation; that such evidence of inflammation as can be noted elsewhere in the body is frequently masked by the cyclical changes; that when inflammation is actually present (as shown by plasma cells), there may be no clinical signs of "endometritis," and, on the other hand, that when all the signs of "endometritis" occur no morphological evidence of inflammation may be noted.

On the other hand, all changes, both morphological and clinical, can be accounted for by purely ovarian disturbances which escape anatomical observation, but may be studied by physiological methods—castration, X-Ray of ovaries.

At the present time it is more important to offer a simple and reliable guide to the pathologist for use in making his report on curettings, etc., than to take any fixed and irreconcilable stand in regard to a mooted question. The following plan is offered for use in making reports.

I. (1) A *premenstrual* or *secretory* stage.
   (2) A stage of *menstruation* (it will be found that mucosae from cases of menorrhagia and metrorrhagia alike conform to this type), and
   (3) an *interval* or *stage of comparative rest.*

Curettings of these types should be reported as "normal endometrium," with mention of the appropriate stage, regardless of whether the stage conforms accurately with the date of menstruation.

II. If, in addition, plasma cells are found, it is sufficient to report "endometrium, showing chronic inflammation" and "cyclical stage 1, 2 or 3," as the case may be.

III. Borderline cases between physiological and pathological growth can be classified as "endometrium with exaggerated phase," in order to emphasize the fact that the change is purely secondary (ovarian influence).

IV. Marked glandular cystic hyperplasia, hyperplasia after the menopause, etc., can be reported as such without the use of the word "endometritis."

TWO CASES OF INFECTION WITH LAMBLIA INTESTINALIS.*

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The Lamblia Intestinalis or Megastoma Entericum seems to be a fairly common parasite in Europe, but in America it has been reported only three times. Lambl[1] found the organism first and called it Cercomonas Intestinalis. Later Grassi[2] and others in Italy found that it was not an unusual parasite in cases of intestinal trouble. Moritz and Hölzl[3] made an extensive study of the subject and found the organisms in the stools of half a dozen patients suffering from diarrhoea and in the duodenums of ten tubercular patients who came to autopsy. Paul Cohnheim[4], in Berlin, reports the parasites in the stomach contents of several cases of carcinoma ventriculi and in the stools of five patients with diarrhoea and also in three normal individuals.

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*Since this report was read before the Society, Lamblia cysts have been found by Mr. John E. Ray, Jr., a senior student of the Cornell University Medical College, in the feces of a baby four months old. The writers have also found them in a boy seven years old who has suffered from diarrhoea. His R. B. C. are 4,500,000; Haemoglobin, 82 per cent.

About a dozen other writers have reported cases from Italy, Germany, Russia and Sweden. Stiles[5], ten years ago, reported the first American case, a patient of Dr. Hemmeter in Baltimore. Emerson[6] has described in his text book a case from the wards of the Johns Hopkins Hospital. Allen[7] has recently found the Lamblia in a negro girl with diarrhoea who has never been out of Charlotte, N. C. The organism has also been found in mice, rats, rabbits, cats, dogs and sheep, and is probably transmitted to man through dust or food contaminated by the excreta of these animals.

The Lamblia belongs to the family of Flagellata and shows four pairs of flagellae. The motile form of the parasite is kite shaped and measures 10-21 m. in length and 5-12 m. in breadth. There is a curious sucker-like mouth which is kidney shaped when seen from the front and concave when seen from the side. The nucleus is divided into two oval bodies which are sometimes united by a bridge. The flagellae causes a rapid, aimless motion sometimes making the organism turn over and over as it crosses the field of vision.

Apparently the motile forms occur in great numbers in the duodenum where they attach themselves to the mucosa by means of their sucker-like mouths. When carried from the duodenum into the lower intestine, they become encysted unless they are hurried along by catharsis or diarrhoea. Under the microscope the process of encysting can be readily observed. The cysts are oval, slightly refractile and measure 10 x 7 m. Sometimes they appear structureless, but more often one can see lines indicating former flagellae or oval bodies indicating the halves of the nucleus.

While the Lamblia has been found in normal individuals, it has much more often been found in children and adults suffering from chronic intestinal indigestion. Most observers consider it harmless, but others are inclined to believe that it can start or keep up the condition. Some believe that the parasites, which are often present in enormous numbers, can cover so much mucous membrane as to interfere with the absorption of foods.

It seems to be rather difficult to get rid of the Lamblia. Those who have made persistent attempts have found that calomel in small doses is almost the only cure. In some cases the infection lasts for years.

America has so many immigrants from countries infected with the Lamblia that one would expect to find it often in our hospitals. While it is an easy parasite to overlook in an ordinary routine examination, it would certainly be discovered by any one searching for amoebae.

The two cases here presented were probably infected in Europe. They are brothers, five years and three and one-half years old. The children of American parents, they have spent most of their lives in Paris, being taken on motor trips through Northern Italy, Switzerland and Southern Germany in the summers. Two years ago, the younger boy began to have a distended abdomen. One year ago, the elder boy also began to have intestinal indigestion. Last summer they came back to this country and were seen by us just as they were getting over mild attacks of whooping cough. Both boys were in fairly good condition, but were losing weight. Their appetites were capricious, their bowels irregular, their stools foul smelling and their urines loaded with indican. There was no mucus in their stools and Schmidt's fermentation test was negative. Both boys showed 80 per cent. Haemoglobin. In November encysted Lamblia were found in their feces and the children were put on a moderately restricted diet in order to clear up the intestinal indigestion. In December they were started on small doses of calomel, followed by magnesium citrate twice a week. Now, in February, 1912, their appetites are improved and the younger boy is gaining weight. The older boy still has some intestinal indigestion.

The stools of the younger boy have from the first shown Lamblia cysts. Before the calomel they were present in enormous numbers, averaging perhaps two cysts to a No. 7 Leitz field. Since the calomel, the cysts have been fewer, and in the last specimen were hard to find.

The older boy on the first two examinations showed no cysts. Later they appeared in large numbers. Shortly after calomel was started, they disappeared for a time, but the last examination showed them present again.

In both cases kite-shaped forms were found only when a laxative was given and the stool examined on a warm slide as soon as it was passed. Only a few actively motile forms were found after a prolonged search.

Summary: The Lamblia Intestinalis is a parasite of doubtful pathogenicity which is fairly common in Europe, but seldom found in America. Possibly it is overlooked on account of the fact that it usually appears in the cyst form, which is very small and not unlike some vegetable cells. The two cases here reported, the fourth and fifth in this country, were probably infected in Europe.

Discussion.

DR. I. ADLER: I would like to ask whether there is any eosinophilia in the blood. As a rule, and as yet unexplained, all the intestinal rhizopods, such as amoebae and the like, produce no eosinophilia, while the flagellatae, as far, at least, as is known to me, are usually associated with considerable eosinophilia in the current blood.

DR. MARTLAND: I have a case of infection with Lamblia at the present time, which was referred to me by Dr. John B. Murphy, of Chicago, for the purpose of making repeated examinations of the feces for trichomonas intestinalis and tubercle bacilli. The patient is a single woman, about 25 years of age, who has had an obstinate diarrhoea of over six years' duration. She had consulted several physicians in New York, Chicago and abroad, and spent a large part of this time in private hospitals and sanitoria. She had had repeated examinations of the urine, feces and gastric analysis made.

I first exmined her specimen of feces for five successive days and at all times the stools were loose; there was no formation of scybalae at all. At all times there was found an enormous number of the flagellated forms, together with a very large number of the encysted forms.

The patient was ordered to bed for ten days and kept on sterile food, consisting mostly of milk. She took an enema, morning and night, in the knee chest position, consisting of 3 pints of hot water containing 8 grs. of methylene blue.

A capsule was given, one hour after each meal, three times a day, consisting of:

Methylene blue	gr. 3
Quinine tannate	gr. 2
Bismuth subgallate	gr. 10

In addition, calomel, gr. 1/30, was given, one hour after meals, three times a day, on the first day, skipped for three days and repeated in a like manner.

At the end of ten days the feces were examined for four successive days, and no Lamblia were found, the patient being on regular diet, and the medication stopped.

A second similar course of treatment was pursued for another ten days, and negative examinations resulted.

The patient is now remaining in bed, and taking saline enemas twice a day, and large doses of bismuth subcarbonate.

She has been constipated most of the time, with several well formed stools and no Lamblia can be found.

She had no eosinophilia.

DR. W. G. MACCALLUM: It seems to me, for our instruction, it would perhaps be easier to find out what it was that cured the patient, if you gave one thing at a time.

What, Dr. Du Bois, have you learned further, if anything, as to the study of the tissues? Has there been a single case investigated as far as the intestinal wall? Is there any further history of this Lamblia other than the two stages—the encysted and the actively motile form?

DR. DU BOIS: Only one man, Zabel, *Arch. f. Verdaungskrankheiten*, vii, 1901, p. 509, I believe, has published description of sections after autopsy. He shows elaborate pictures of the Lamblia attached to the mucosa by the flagellae. There is no evidence of stages other than the cyst form and the motile form. Grassi swallowed some of the cysts and later developed an infection with the organism.

We regret to say that eosinophiles were not counted in these two cases. In other reported cases the eosinophile count has not been increased.

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PNEUMONIA AND ABSCESS OF THE LUNG IN A CHILD.

W. P. NORTHRUP, M.D.

I think this case is of some value as showing how the demands of the clinician were at once answered by the autopsy maker. The presentation consists mostly of the X-ray pictures which demand that certain things shall be found and that they were subsequently found.

This case is a child 17 months old; was sick 21 days in the hospital, was sick 3 days before, making 24 days of sickness. First stage ordinary cold—coughing, sneezing, and hoarseness.

Then it enters upon a second stage quite different from the first; the child showed symptoms of a sepsis. Child became very sick —pulse was rapid, respiration increased; the temperature reached in these next 11 days 106°, fluctuating from 101° to 106°. At the end of this second period of fluctuating septic temperature with prostration, the child entered upon a third stage, namely, a stage which was more or less uniform, steady temperature—high, 104°, with disturbed respiration—pulse ratio, and went four or five days upon this distinctly pneumonic course, with symptoms of developing broncho-pneumonia. It later went on to a fourth stage in which the child seemed to pass a crisis, to improve and promise to get well; and then it died.

The first stage I have no X-ray picture of, the ordinary cold; the second stage I have a distinct picture of—the heart side has distinctly a shadow of consolidation. The child came to the hospital at the beginning of the second period. We believe this circumscribed shadow to be an abscess. It does not touch the heart; it lies just in the plane which you see. Then, in order to find out how deep it was we went to work and took one lateral picture. The abscess shadow lies in the very center of the lungs.

It was perfectly obvious that the child was prostrated by a very severe illness. We fancied there was an associated influenza. We made the diagnosis of abscess due to influenza bacillus. We proceeded to put in a needle and could find absolutely nothing. After a little we took another picture; here, you see, is the third stage; that is distinctly a pneumonia, a very extensive shadow. Now there is a fourth stage in which there was very much more pneumonia, which we could not picture because the child was too ill to allow it. There was evidently an abscess, but we could not find it. We searched the mouth and sputum and everything we could get up from coughing we sent to the laboratory, but could find nothing. But to me it seemed perfectly obvious that there was an infection of influenza. We believed the abscess was probably due to an influenza. Then it went on, as I said, to a case of pneumonia, and after it had seemed to be on recovery from pneumonia, almost like a crisis, it suddenly died.

Immdeiately after death, fearing that we might not get an autopsy, I got a very large needle and probed in every direction, with those X-rays before me. In the autopsy, to my great satisfaction, they did find two abscesses about the size of beans, that is, they were technically abscesses, but they were not large enough to satisfy me. This first shadow was fully accounted for by what we found at autopsy, namely, these little cavities, and all about little necrotic areas with a little tissue between not yet broken down. There was a formation of partially organized fibrin within the alveoli.

So, looking backwards, we feel satisfied that our first diagnosis verified that the primary lesion was influenza, with an influenzal abscess, and the pneumonia a secondary development. I believe the only lesions of the body were in the lungs.

Discussion.

Dr. MacCallum had performed the autopsy for Dr. Northrup and found that there was extensive consolidation of nearly all of the upper lobe of the lung, which was curiously mottled with opaque yellow patches. There were numerous holes in the pleura produced by the needle. On section the opaque areas had extended into the lung and in places showed liquifaction of their central portions.

Dr. Soper was able to discover two types of bacteria—pneumococcus and influenza bacillus. The latter grew in the first culture but could not be grown again. Histologically, the lung shows lobular pneumonia in certain areas, of which there is necrosis of the tissue and liquefaction. It resembles the condition seen occasionally in acute glanders of the lungs. About these areas there are alveoli in which the fibrin has assumed a very solid form and has become organized by an invasion of connective tissue cells.

CHOLESTEATOMA OF HORSE'S BRAIN.

ELI MOSCHCOWITZ, M.D.

The horse had given symptoms of blind staggers for some weeks previous to death. After a delirious attack in which he smashed four stalls, he was shot.

At autopsy, both lateral ventricles were completely filled with masses which fitted accurately into the cavity. These could be removed and replaced, like a ball in a socket. On the left side the mass was attached by a thin thread to the pia; on the right side the mass lay entirely free. Both masses were practically identical in shape and structure. They were the size of a hen's egg, ovoid in shape, and perfectly smooth. They were white in color, both externally and on section. The consistence was soft, and on section the cut surface was smooth, slightly granular, and uniform.

Microscopic examination revealed a thin fibrous capsule and a stroma which consisted by loosely distributed small, round cells, cells of the plasma type, and a considerable number of polymorphonuclear leukocytes. The tumor was rich in small, well-formed blood-vessels. Throughout the section are numerous spaces discreetly distributed. These spaces are large and are made up of smaller wedge-shaped spaces, which are in a parallel or fan-like arrangement. The spans are empty in the stained specimen, but are filled with closely wedged cholesterin crystals in the frozen section.

According to Kitt (*Pathologie der Tieren*), these tumors are known among veterinarians as "cholesteatoma vasculosa," although they do not resemble in the slightest way the cholesteatoma met with in the human being. The true nature of these growths is not known. Certainly, the microscopic picture and the physical characteristics strongly suggest an inflammatory origin, and this is further corroborated by the fact that these growths frequently occur in cases of chronic glanders and streptococcus inflammations of the nose.

CASE OF CONGENITAL OBLITERATION OF THE BILE DUCTS.

ELI MOSCHCOWITZ, M.D.

The patient was a three months old female child and was jaundiced from birth. The jaundice at the time of death was deep, although the skin was not green. The child gained very slowly, although it was breast fed, and did not appear or behave very ill until about 24 hours after admission, when the child began to vomit frequently and soon succumbed. Dr. Alfred F. Hess, during life, demonstrated pancreatic ferments with the aid of his duodenal catheter, and diagnosed congenital obliteration of the bile ducts.

At the autopsy, this diagnosis was entirely confirmed. The gall bladder was almost completely obliterated, only a small lumen, holding about a drop of clear watery fluid, persisting. The hepatic, cystic and common bile ducts were completely obliterated and were transformed into dense fibrous cords. In the duodenum there were two papillae. The upper corresponded to the obliterated common duct and was completely obliterated. The lower, about half an inch from the upper, showed a small opening which led into the Duct of Wirsung. The liver was enlarged, firm, and dark-green in color. The surface was slightly nodular. On cut section a distinct cirrhosis was apparent. There was no gross dilatation of the intrahepatic bile ducts. The portal vein and hepatic artery were normal. The spleen was slightly enlarged. The pancreas, kidneys and intestines were normal.

Microscopic examination showed a marked increase of the periportal connective tissue with an abundant new formation of bile ducts. The intracellular bile ducts were greatly dilated and filled with green masses of bile. The parenchyma was otherwise normal. Sections of the other organs showed nothing noteworthy.

ON THE PRE-CANCEROUS STATE—AN EXPERIMENTAL STUDY.

I. LEVIN, M.D.

By a pre-cancerous state we understand a condition of chronic inflammation or other abnormality of the tissue in which cancer develops. This condition immediately preceding the growth of the tumor, presumably has, at the same time, a causative relationship to the development of the cancer. The following points must be considered in the study of the pre-cancerous state: In the first place, does the condition found on morphological study of the early stages of cancer actually have a causative relationship to the development of cancer? Further, does the change in the tissue always take place in the beginning of a cancer growth? And, third, which changes in the tissue are to be interpreted as a pre-cancerous state?

The region in which cancer develops consists of two parts—the group of proliferating cells and the normal tissue surrounding the cancer.

Now, under the term "the pre-cancerous state" one may understand an abnormal condition of a group of cells which are subsequently transformed into cancer cells, or a change in the normal tissue surrounding the growing cancer. While at present most investigators admit the existence of a pre-cancerous state, the opinion is divided as to which part of the tissue is involved in the process.

The school of Ribbert and his pupils consider practically only the changed condition in the tissue surrounding the growing cancer; they claimed, until very recently, that any normal cell may become cancerous provided the condition of the surrounding tissue is favorable to it. On the other hand, Hansemann, Orth and other writers maintain that only the cell which subsequently becomes cancerous undergoes a pre-cancerous change. They claim that a normal body cell must undergo certain preliminary changes before it becomes cancerous.

In his recent article on the different conditions of the pre-cancerous state. Orth distinctly states that the condition of the surrounding tissue has nothing to do with the development of cancer. Only that group of epithelial cells which subsequently develop into cancer undergoes a preliminary pre-cancerous change.

The morphological study of human material cannot settle the divergence of the opinions. The tissue surrounding a growing cancer may be changed, but it is impossible to ascertain whether the surrounding tissue first becomes abnormal and then the cancer develops or whether the cancer development influences the surrounding tissue and it consequently becomes abnormal.

There seems to be more promise in the study of the subject when the material to be used is the transplanted cancer in animals. It is true that here we can consider only the conditions of the surrounding tissues. The group of cancer cells is brought from outside preformed. Consequently we cannot study by the aid of experimentation a pre-cancerous state which would consist in a changed condition of normal cells which subsequently transform into cancer. The existence of such a pre-cancerous state is impossible, as Orth states, to ascertain until the time that we can artificially produce cancer from normal cells. One must confine himself, then, only to the condition of the tissue surrounding the growing cancer cells. The condition of the surrounding tissue is apparently of utmost importance in the development of cancer, since animal study has shown that an inoculation of the same tumor tissue completely fails in a certain number of animals. This phenomenon must be due to the fact that the tissue surrounding the inoculated tumor reacts differently in different animals. This reaction is general in its nature and affects the whole organism of the host. Now, if it were possible to find conditions in the same animals where a local inhibiting influence may be exerted upon an inoculated cancer, while the rest of the animal is apparently susceptible to the growth of the cancer, such a condition would show the existence of a pre-cancerous state as a condition of the normal tissue surrounding the cancer.

In view of this idea, and in view, furthermore, of the fact that my former studies on inoculation of cancer in different organs showed that while Ribbert's ideas on the value of a reaction of the surrounding tissue may be right, this influence does not consist in a new formation of connective tissue surrounding the growing cancer, and it seemed of importance to search for local influences of the normal tissue upon a growing cancer. During the course of studies on inoculation of cancer in different organs, a tumor was found, an adeno-carcinoma of a rat, which, while it readily grows when inoculated into animals subcutaneously, fails to grow when inoculated into a normal testicle. Here, then, was a purely local condition of resistance of a certain tissue to growth and development of cancer. The question occurred whether it were not possible to change the condition in that special organ in such a way as to render it susceptible, artificially, to the growth of cancer. The experiments consisted in the following three series:

First: To prove positively the contention that the cancer would not grow in a normal testicle, forty animals were inoculated and only in one of the animals did the tumor grow. The testicles were all examined microscopically; most of them showed a peculiar condition of complete necrosis of the testicular tissue and complete disappearance of the inoculated tumor.

Next the testicles were treated with certain substances previous to the inoculation. Scharlach R oil was injected into the testicle. The organ upon the injection changed so that there occurred a great deal of new connective tissue formation and besides the epithelial elements were changed to a greater or lesser degree. In some testicles the tubular cells were practically normal, but surrounded by a great deal of connective tissue. In others the tubules were greatly changed, the cells were in a state of coagulative necrosis, and the structure of the tubules was practically gone. Now, of the thirty-two testicles that were thus treated, subsequent inoculation of tumor was successful in nine testicles, *i. e.*, in 28 per cent. of the animals used. The most interesting phenomenon in connection with this series consisted in the fact that tumor growth took place in these testicles where the change of the cellular elements of the tubules was the greatest, *i. e.*, where the epithelial cells were in a state of necrosis. In the other testicles where there was just as extensive connective tissue formation but where the cells in the tubules were normal, the tumor did not grow.

The third series of experiments consisted in an injection into the testicle of a 4 per cent. emulsion of ether in water. The experiment was repeated on twenty animals in the testicle. This substance apparently produces a greater lesion in the testicle than Scharlach R oil. While the connective tissue growth was just as extensive as in the testicle treated with Scharlach R oil, in these testicles one finds a great deal more frequently complete degeneration and necrosis of the cellular elements of the tubules. Of the twenty testicles treated previously with ether water, the tumor grew in 65 per cent. of the animals used.

Thus the three series of experiments represent a condition where a normal testicle resists the growth of inoculated cancer while the animal itself is apparently susceptible, and, furthermore, it is possible, artificially, to change the condition of the testicle so that the organ tissue is artificially rendered susceptible to the development of cancer.

LANTERN-SLIDE DEMONSTRATION.

It seems then that we succeeded here in inducing artificially in the testicle a pre-cancerous state by, *i. e.*, a state of the tissue surrounding the tumor graft which renders it susceptible to the growth of inoculated cancer. These experiments also show clearly that this condition of local susceptibility, the pre-cancerous state, is not due to the development of newly-formed or changed connective tissue surrounding the tumor growth, but consists primarily in a certain change of the parenchymatous cells of the organ, a change which removes its inhibiting power against the growth of cancer. It would thus seem that Ribbert's ideas may have to be changed, that the connective tissue change is not specific or primary in the pre-cancerous state, and that the "pre-cancerous" impairment of the normal resistance of parenchymatous cells is of great importance in the development of cancer.

Discussion.

Dr. MacCallum had felt some hesitation in using the term "pre-cancerous stage" and had suggested to Dr. Levin that "pre-cancerous state" was at least preferable. It seems possible to regard this production of fibrous tissue, etc., as the establishment of a locus minoris resistentiae such as may give rise to the development of a localization for bacteria in places where otherwise these bacteria would not tend to produce lesions. The discussion leaves out of consideration entirely for the moment the obvious fact that the cancer cells are cells of very different biological characters than the normal.

THE SIGNIFICANCE OF THE PATHOLOGICAL OCCURRENCE OF ANISOTROPIC LIPOIDS.

FREDERICK HANES, M.D.

No one contends to-day that the fat which is so constantly found in injured cells is directly derived from a degeneration of the cell. Researches of the past few years have proven that the presence of excessive amounts of fat in cells is always due to a process of accumulation or infiltration. The acceptance of this conception has aided greatly in the elucidation of a problem which has been generally misunderstood since the time of Virchow.

It is to another and newer phase of the question of fat infiltration, however, that I wish to direct attention this evening. In 1902 Kaiserling and Orgler (*Virch. Arch.* 167, 296) while studying the fat in the kidney in a case of chronic parenchymatous nephritis, discovered that some of the fat was not neutral fat, for when placed between the crossed Nicol prisms of a polarizing microscope, it was doubly refractile, anisotropous, whereas neutral fats are isotropous. Mettenheimer many years before had made similar observations, and after him Beneke and Apathy.

Kaiserling and Orgler studied the occurrence of these anisotropous fatty substances under physiological and pathological conditions. They found that the fats of the adrenal cortex were in part anisotropous and that they belonged to the class of substances which Overton has called lipoids. In 1910 Aschoff (*Ziegler's Beiträge*, 1910, 47) summarized the previous work of others upon the question of the accumulation of lipoids in the tissues under various pathological conditions, and on the basis of his own and Adami's investigations he was able to say that the anisotropous lipoid substances found in the body are usually esters of cholesterol. Other lipoids may show anisotropism, but cholesterol esters are the only ones which constantly do at body temperature. Aschoff therefore divides fat infiltration into glyceryl ester, and cholesterol ester infiltration. He recognized the possibility of a third type due to infiltrations with other lipoids (lecithin, etc.), but owing to the rudimentary condition of our chemical and pathological knowledge of these substances he did not discuss them in detail.

Kawamura (*Die Cholesterinesterverfettung, Fischer*, 1911), a pupil of Aschoff, has developed the conception of cholesterol ester infiltration in a monograph to which I must refer you for details.

This hasty and imperfect summary of some of the more outstanding contributions will serve to direct your attention to this newly developed phase of fat infiltration, and full literature lists will be found in the articles mentoined, especially in the monograph of Kawamura.

In the limited time at my disposal, I can only refer to two points of interest in regard to the anisotropic lipoids, namely, their optical properties, and the pathological significance of their occurrence. If some of the detritus of an atheromatous patch in the aorta be examined between crossed Nicol prisms, one sees many small spherical bodies divided by a dark maltese cross into four brilliantly illuminated sectors, that is, they are anisotropous. Such globules, according to the careful researches of Lehmann and Schenck, are fluid crystals. They are of a fatty nature and are regarded by Aschoff and Kawamura as esters of cholesterol, probably cholesteryl oleate.

In the demonstration room I have placed a polarizing microscope fitted with a Reichert warm stage which is supplied by a syphon arrangement with either hot or cold water as desired. If, while examining these brilliant fluid crystals, one allows hot water to flow through the stage, the beautiful anisotropic phenomenon gradually disappears and the entire field becomes dark. The thermometer shows that the globules pass from the fluid crystalline, anisotropous phase into the fluid, isotropous phase at near 40° C. If one now allows cold water to flow through the stage, the former brilliant picture is restored; the globules have assumed the fluid-crystalline form again. This is truly a remarkable phenomenon, but one which fortunately for us is perfectly familiar to physical chemists, who have carefully studied many such fluid crystalline bodies. I must refer you for details to the excellent monograph of Schenck on "Kristallinische Flüssigkeiten u. flüssige Kristalle" (Leipzig, Englemann, 1905).

Aschoff and Kawamura think the heat phenomenon just described is characteristic of cholesteryl esters, and it thus affords a quick and easy method for their recognition. The problem is new, however, so generalizations should be accepted with critical caution.

As to the pathological significance of the finding of such anisotropic lipoids in the tissues, all writers are agreed that they only occur in connection with chronic processes associated with cellular necrobiosis. They do not occur in frankly acute processes. They have been found, for example, in atheroma, chronic nephritis, chronic salpingitis, in many pyogenic processes, actinomycosis, many tumors, especially hypernephromata, etc. (vide Aschoff).

The macroscopic and microscopic recognition of these substances would seem to offer a diagnostic aid in many conditions, and every pathologist should familiarize himself with the properties and occurrence of these anisotropic lipoids.

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Dr. W. G. MacCallum, *President.*

REPORT OF THE COMMITTEE ON MICROSCOPY ON DR. JESSUP'S SPECIMENS OF PLASMA CELL TUMOR OF THE TONGUE.

We are disinclined to regard the process as a neoplasm and offer the diagnosis of *chronic granuloma* of unknown origin, for the following reasons:

The long duration of the process.

The wide local dissemination of the lesion.

The existence of a process in the rectum, probably of identical nature.

The microscopical picture is that of a granuloma, not a true neoplasm. The cells are of typical form without excess of chromatin or marked variation in size. They loosely infiltrate the perivascular tissues, fat tissue, and muscle bundles. The lymphocytic or plasma cell infiltration is chiefly superficial, suggesting the action of an irritant passing in from the surface.

The muscle tissue shows extensive degeneration followed by fibrosis, and foci of fibrosis appear in the wide cellular areas. These changes in the muscle, especially, seem to us incompatible with the diagnosis of sarcoma and to indicate the inflammatory nature of the process. The entire lesion suggests the possibility that there was some obstruction to the circulation in the deeper portions of the tissue not included in the sections.

DEMONSTRATION OF SPECIMEN OF MEGACOLON.

CHARLES NORRIS, M.D.

Dr. Charles Norris presented a case of Congenital Megacolon or Hirchsprung's Disease. The case will be reported in detail by Dr. Wilcox.

The specimen came from a male child 18 months of age, who had been subject to constipation since the age of three weeks; for the past year had been treated at dispensaries for constipation. There were no natural movements during his week's stay in the hospital. The abdomen was greatly distended, the abdominal wall being very thin, due to extreme stretching. On cutting through the abdominal wall, the entire upper portion of the abdomen was occupied by a greatly distended transverse colon and coecum. The dilatation ceased abruptly at the splenic flexure, the descending colon and sigmoid being of normal appearance and dimensions. The dilatation commenced in the coecum at the ileo-coecal valve, the small intestines being normal. The dilatation is greatest at the middle portion of the transverse colon, the gut being in this situation 21 cm. in diameter. Wall of the dilated gut is thickened, its mucous membrane is everywhere smooth, showing in a few places patchy, mucosal hemorrhage. The gut contained a large amount of extremely frothy material which was light colored and greasy. At the splenic flexure there was a valve-like fold at the junction of the distended and undistended portions of the colon. Dr. Norris considered that there was a partial valve-like closure at the splenic flexure which had led slowly to the distention and hypertrophy of the gut. Sections taken from the distended gut show marked hypertrophy of the muscular coats, mucous membrane being normal except for the hemorrhagic spots referred to above. The other organs showed no lesions of interest. The case is an unusual one for the reason that the sigmoid flexure was not involved.

Dr. Norris presented a series of large intestines, showing different lesions of this portion of the gut, namely, a case of Suppurative Colitis; a case of Ulcerative Amoebic Colitis; a case of Chronic Suppurative Typhlitis, which was discovered in a patient dying of hemorrhage from the rupture of a blood-vessel at the base of a typical round ulcer of the duodenum; and an interesting case of Acute Phlegmonous Typhlitis in a colored man forty years of age, in which Bacillus Coli Communis was obtained in pure culture from the spleen; there was, besides the lesion of the gut, a typical atrophic cirrhosis of the liver with an extremely small left lobe, which was considered to be an anomaly.

Discussion.

Dr. F. C. Wood thought that it was interesting to realize how very rarely these cases of terminal colitis in nephritis are recognized clinically. He had never seen one positively diagnosed before death. If the stools were carefully examined it should be easy to make the diagnosis, because there must be a considerable amount of blood, debris, and mucus.

Dr. MacCallum thought that the liver which Dr. Norris exhibited showed changes similar to those described by himself some years before. The atrophy of the left lobe might be regarded as the effect of a toxic or infectious injury rather than a congenital anomaly on account of the large size of the afferent portal vein. He suggested that it would be interesting to know whether there were evidences of a regenerative hypertrophy in the right lobe.

Phlegmonous colitis is a condition which has been recorded relatively seldom but seems to resemble in its mode of production the other forms of phlegmonous enteritis which sometimes occur higher up in the intestine. In cases which he had observed almost every one showed streptococci in the submucosa with minute perforations of the mucosa itself.

Dr. Charles Norris: I am very sorry that I have neglected to cut the left lobe of the liver; I will do so as soon as I can. Of course, it is very true that colitis is often an accidental finding and it is especially so in the cases where there is ulceration near or involving the rectum. In this case, the diagnosis was not made at all, although the ulcers at autopsy were near the marginal ring.

A SIMPLE METHOD FOR OBTAINING THE ALPHA-NAPHTHOL OXIDASE REACTION IN LEUCOCYTES.

FRANCIS CARTER WOOD, M.D.

Recent studies of so-called acute lymphatic leukemia by Longcope, Schultze, and others have shown that some of the large cells previously considered to be leucocytes carry an oxidase ferment easily demonstrable by certain reagents. The substances usually employed are a 1 per cent. aqueous para-dimethylphenylendiamin (also known as para-amidodimethylanilin) and a saturated aqueous solution of alpha-naphthol. Equal volumes of these solutions are mixed and poured over a slide which has previously been fixed with formalin, not with alcohol. Old smears do not require any fixation. Bone marrow cells carrying the oxidase ferment take a brilliant blue stain under these conditions, the dye affecting the granules chiefly. The lymphocytes do not show any color.

In a study of a number of cases I have found it difficult to keep the free base which is ordinarily recommended, and this trouble has also led to the suggestion in Germany that the amount of the para-amidodimethylanilin required for each test should be obtained sealed in glass tubes. It is possible, however, to avoid this difficulty by a very simple procedure. While the base and the hydrochloride of para-amidodimethylanilin are difficult substances to keep and handle, the sulphate, which is easily made up synthetically by the reduction of the indicator methyl orange either with stannous chloride[1] or, as suggested by Fischer[2], with ammonium sulphide, is a crystalline dry powder which is very easily measured out or weighed in small amounts, and has kept perfectly in a stoppered bottle for several years in my experience. A small quantity of this powder is dissolved in about 1 to 2 c.c. of normal sodium hydrate. The alkali decomposes the salt, setting free the base. An equal volume of 1% aqueous alpha-naphthol is added, and the mixture is ready for use. The presence of such a considerable quantity of alkali does not interfere with the reaction but rather hastens it. Within a few seconds after the reagent has been poured on the slide, the bone marrow cells will take a deep blue color. If the reaction is too rapid, 1.5 c.c. of normal acid can be added to neutralize the alkali partially, but I have found the solution in normal sodium hydrate to be perfectly satisfactory.

[1] GATTERMANN: *Die Praxis des organischen Chemikers.*

[2] FISCHER: *Ber. d. deutsch chem. Gesellsch.*, 1883, xvi, 2234.

UNUSUAL TUMOR OF THE LYMPH NODES.

FRANCIS CARTER WOOD, M.D.

This specimen is one of considerable interest from both the diagnostic and the prognostic aspects. It consists of several moderate sized lymph nodes removed from the axilla of a patient otherwise perfectly healthy. Clinically the case is one of typical Hodgkins' disease, showing some anemia but no other disturbances. The nodes were encapsulated and freely movable. On section they were rather opaque and showed no necrosis.

Microscopically the nodes are composed largely of cells of an epithelial or endothelial type lying in strands and masses throughout the tissue. There is no connective tissue about the individual cells. Some of the normal lymph structures are still retained; the germinal centers show well in some of the sections; and there are areas of perfectly normal lymph tissue. Some of the peripheral sinuses are completely filled with cells of the tumor and these cells are also to be found in some of the blood vessels in the capsule. There are also strands of the cells in the somewhat thickened capsule itself. There is very little connective tissue reaction in the nodes, not nearly as much as is generally seen in Hodgkin's disease. Occasionally mitoses are found in the large cells. Some of these cells are multinucleated, resembling very much the large cells of Hodgkin's disease. There are no eosinophile cells in the tissues. No bacteria could be demonstrated after softening some of the tissue with antiformin.

It is not easy to make a definite diagnosis on this material, and I feel that much must be decided by the clinical course of the case. One pathologist who has seen the specimen is quite certain that it is a case of Hodgkin's disease in a rather early stage; others, including Dr. William H. Welch, have considered the specimen to be of a sarcomatous nature. I have never seen a tumor exactly like this in morphology, though some ten or twelve years ago a somewhat similar specimen came into my possession, but in that the vascular development was considerably greater and the cells were arranged in close contact with capillaries, suggesting hemangiosarcoma. The invasion of the node also was less diffuse and more nodular than in this case.

Very little of similar cases can be learned from the literature on Hodgkin's disease or sarcoma of the nodes. A few cases, probably similar to this, have been described, but inasmuch as the reports are illustrated by drawings and not by photographs it is difficult to say just how close the resemblance is. Personally, I am rather inclined to consider this a cellular hyperplasia of a tumor nature, but it is not impossible that the case will finally develop into a typical Hodgkin's, with lesions in other nodes.

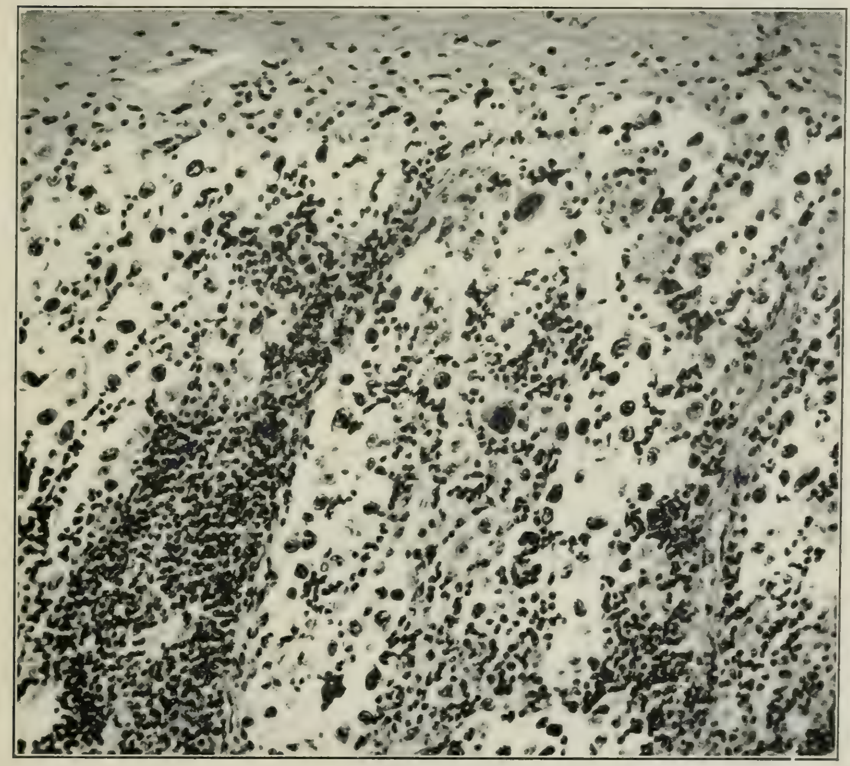

FIG. 1—Section from the periphery of lymph node, showing large cells filling sinuses. (x 250.)

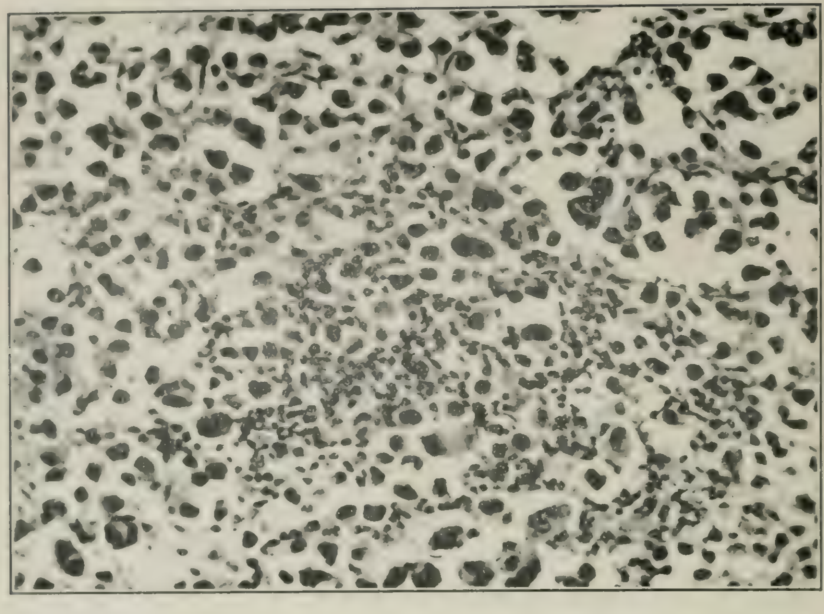

FIG. 2.—Alveolar portion of growth replacing the lymph structure. (x 250.)

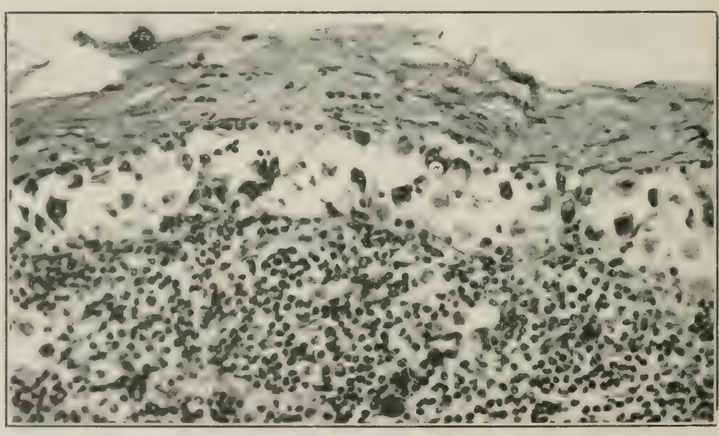

FIG. 3. Invasion of peripheral sinus of lymph node of cells. (x 250.)

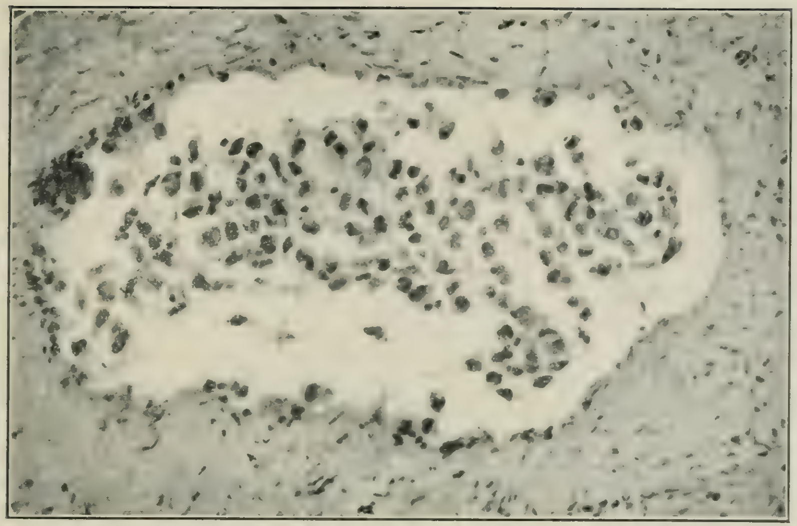

FIG. 4.—Blood vessel in perinodular fat with lumen filled with large cells of of the same type as the tumor. (x 250.)

A CASE OF SO-CALLED "KRUKENBERG'S" TUMOR OF THE OVARY.

MORTON E. HALL, M.D.

I wish to present a very interesting case of malignant tumor of the ovary which resembles in its histology the so-called Krukenberg tumors of the ovary. To Dr. Arthur Reich I am much indebted for obtaining an accurate and concise clinical history of the case as follows:

The case was brought to Bellevue Hospital in a serious condition on February 1st, 1912. Clinical history: Nellie D., age 32, married, native of England, a trained nurse; for past two or three years had been working as a cook; previous history not obtainable. Is pregnant approximately twenty weeks; according to husband she had become dull and made incoherent statements, had severe morning vomiting for the past five months of the pregnancy. No loss of weight was noted.

For past two weeks patient had been vomiting and had great epigastric distress. For forty-eight hours prior to admission, she was in a semi-comatose condition, had severe headaches.

On admission patient was irrational, presenting the picture of a psychosis. Skin and mucous membranes were markedly dry, conjunctivae intensely inflamed; considerable emaciation; no oedema. Had general abdominal pain without any particular points of tenderness or rigidity. Height of fundus was 5 cm. below umbilicus. No foetal heart sounds heard but foetus could be palpated. Cervix was large and soft; external os not dilated. Posterior fornix was thickened and firm.

Temperature on admission was 97.3 and ranged between 97-99.2. Pulse 72-100, of poor force, low tension and small volume (B. P. .80). Respirations rapid and shallow.

On admission 5 oz. of heavy, dark brownish urine were obtained by catheter, containing albumin and many casts—sp. gr. 1030. During last 58 hours, patient excreted 2 oz. of urine. Patient was catheterized several times with no result. Patient continued in a semi-comatose condition, with delirium, which soon passed into a deep coma, from which she could not be aroused.

Findings after admission: Patient had a convulsion which was general and tonic in character, lasting two minutes. Manual and instrumental dilatation of cervix was performed, and a macerated foetus was extracted of about twenty weeks' gestation. Patient died ten hours after induction of labor. A diagnosis of toxaemia of pregnancy was made.

Autopsy performed by Dr. Charles Norris February 6, 1912, forty-eight hours after death. Body 158 cm. in height, fairly well developed and nourished; there is considerable pallor of the skin; no oedema of the subcutaneous tissues. Breasts are large and contain milk. Peritoneal cavity contains no fluid. There is a moderate amount of panniculus abdominus. Pelvic cavity is nearly filled by the enlarged uterus. On the peritoneal surface of the diaphragm and parietal peritoneum there are extensive flat, firm, whitish, slightly elevated plaques, which are most numerous and largest on the diaphragm and small, circular, 1 to 2 mm. in diameter foci. Lungs everywhere slightly emphysematous and hyperaemic. In the left upper lobe there are a few small areas of lobular pneumonia. There is no evidence of tuberculosis in lungs or lymph nodes. Heart is normal except for slight opacities of the endocardium and a few sub-endocardial petechiae in the left ventricle. Liver shows thickening of capsule and slight chronic congestion. Gall bladder, spleen and pancreas normal. Kidneys are somewhat enlarged and soft; capsule strips readily leaving a smooth surface; cortex is wider than normal, pale and opaque, markings distinct. Pyramids somewhat congested. Uterus is large, 15 cm. in length by 11½ cm. in breadth by 4 cm. in depth; thickness through wall 15 mm. Cavity is packed with iodiform gauze. Placental site is free from clot. Left ovary small and sclerotic, measures 3.3 cm. in length, 1.5 cm. in width and 4 mm. thick at its widest portion, with a few small cysts. Left and right tubes show slightly elevated, pale plaques similar to those seen on parietal peritoneum. Similar plaques are found on the serosa of the broad ligaments and on the posterior wall of the cervix. On section the cervix is infiltrated but the mucosa appears normal. The right ovary is large, 6 cm. in length, 4 cm. in width. It is firm, somewhat hyperaemic; section smooth; there are a few small, subcortical cysts. The isthmus of the uterus is large. There is a large right lateral tear of the cervix and numerous cysts are found on the vaginal surface of the cervix. The vagina and labia are normal. Gastro-intestinal tract; Oesophagus normal; the pyloric portion of the stomach, for several inches, is thickened with a firm, tumor-like tissue and there is considerable hypertrophy of the muscular coat of the pylorus. The regional lymphnodes, the peripancreatic and portals, are infiltrated and there are a number of nodes, which are firm, in the mesentery of the large gut. The small intestine contains a good deal of slate colored mucus without blood. There is considerable hypertrophy of the solitary follicles of the lower portion of the ileum. Lowest Peyer's patch is atrophic but large; mucous membrane of the coecum and transverse colon is extremely congested without ulceration. Rectum normal. Organs of the neck and mouth were not examined. Head: Dura is considerably adherent; there is moderate pial oedema; vessels at the base are normal; no gross lesions of the brain on section. Middle ears and sphenoids normal. The following anatomical diagnosis was made:

Carcinoma of the pylorus of the stomach.
Peritoneal metastases.
Lobular pneumonia.
Acute parenchymatous nephritis.
Acute colitis.
Tumor of the right ovary (endothelioma?)
Postpartum sub-involution of the uterus.
Moderate pial oedema.

Sections of right ovary taken from various parts show a similar microscopic appearance. The outer layer of the ovary is normal ovarian cortex, with a surface layer of low cuboidal cells with deeply staining nuclei (the remains of the germinal epithelium) which in places is absent. The tumor is moderately vascular, consists of a connective tissue stroma composed of fibrils and numerous young spindle shaped connective tissue cells. Lying irregularly among these are large, swollen cells with sickle-shaped nuclei, which are situated at one side of the cell and surrounded by a very small amount of eosinophilic protoplasm. The larger portion of the cell is filled with a homogeneous material, composed of granules (staining with weak aqueous thionin) reddish brown in color. These large cells closely resemble those described by Krukenberg as the signet ring cells. There are also many cells, about a quarter the size of these larger ones, with round nuclei surrounded by eosin staining protoplasm with no evidence of mucin. There are cells which are intermediate in size and shape to those described; they show larger and smaller drops of mucin, surrounded by a ring of eosinophilic protoplasm. Thus we conclude that the signet ring cells are derived from the smaller variety of cells—a conclusion similar to that reached by Krukenberg.

A Van Gieson stain shows the large signet ring cells to be individually surrounded by fine, connective tissue fibrils. This feature led us to believe that we were dealing with a fibro-sarcoma, in which certain of the cells had undergone mucoid degeneration. No normal ovarian tissue was found anywhere in the right ovary.

In the left ovary there was found a small tumor area having a similar microscopic appearance to that described above in the right ovary. There is a sharp line of demarcation between the area of tumor and that of a small corpus luteum cyst.

Sections of the cervix show larger and smaller tumor nodules; the smaller ones are seen to lie in lymph spaces. In no place can any connection be made out between the tumor nodules and the epithelium of the cervix. The smaller nodules show cords of tumor cells distinctly carcinomatous in type. In the larger nodules, however, the central portion shows a structure similar to that described in the ovary, but in the periphery of the nodules one sees cords of rapidly proliferating cells with deeply staining nuclei, which appear to be distinctly carcinomatous. The pelvic lymph-nodes show no evidence of infiltration. Sections of the tube examined, show in the lymph spaces of the serosa a few very small collections of tumor cells, which are carcinomatous in type with no mucoid degeneration.

The peritoneal metastases present a similar microscopic picture. Here the lymph vessels are dilated but none were found with tumor cells. Sections of the pyloric region of the stomach show marked glandular hyperplasia, with acute and chronic inflammatory changes in the mucosa and less marked in the submucosa. There was no evidence of ulceration or infiltration of the mucosa with tumor cells. Muscular layer and submucosa are thickened and infiltrated with tumor cells. Collections of tumor cells vary considerably in size in the serosa of the stomach and in the muscular coat, some being quite large and others small apparently lying in lymph spaces. Collections of tumor cells in the submucosa are very small and in many cases are seen to lie in the lymph vessels. The central portions of the larger nodules with Van Gieson's stain present the same appearance as described in the right tumor. There are many single cells separated by fine fibrils of connective tissue. As one goes towards the periphery of these nodules, the tumor cells appear more in the form of cords with no inter-cellular connective tissue fibrils; their nuclei stain very deeply with hematoxylin and they appear to be proliferating rapidly. The tumor cells in the submucosa in places have broken through the muscularis mucosae but are not directly connected with the acini; in no place is there any evidence of acinal formation in the submucosa. In the central portion of the larger nodules one sees many typical signet ring cells with marked mucoid degeneration and the transitional stages from the smaller cells to the large signet cells. Towards the periphery in the more rapidly growing portions of the nodules no evidence of mucoid degeneration was made out. Sections of the uterus show the uterine wall to be in the stage of subinvolution.

The case is of interest from three points of view: Firstly, Is the tumor in the ovary primary, or is it secondary to a primary tumor of the stomach; secondly, are the tumor cells epithelial or mesenchymal in origin; thirdly, are we justified in applying the word Krukenberg to this tumor, thereby implying that the growth is primary in the ovary, or should this term be used merely to describe the microscopic appearance of the growth in the ovary and similar growths of this organ as described in the literature?

Krukenberg,[1] in 1896, described six cases of malignant tumor of the ovary, characterized by the presence of signet ring cells, which he claimed were different from any other tumor described up to that time. In the two cases in which an autopsy was performed, peritoneal metastases were found, but he makes no particular mention as to the condition of the stomach mucosa. None of his cases showed any evidence of acinal formation and in no case could he find any epithelial origin for the characteristic signet ring cells. He therefore suggested that the cells were derived from the connective tissue stroma of the ovary. Metastases occurred later, by way of the lymph vessels, into the peritoneum and stomach. He described his tumor as a fibro-sarcoma, adding the word Mucocellulare to describe the mucoid degeneration of the cells, and Carcinomatoides to explain the high malignancy and epithelial appearance of the signet ring cells.

Our case resembles Krukenberg's first case in practically all particulars except that mucous membrane of the stomach in our case shows considerable glandular hyperplasia in the region of the tumor. There is no evidence of ulceration and no direct relation of the tumor to the mucosa is traceable.

A review of the literature on this subject is decidedly interesting but it is extremely unsatisfactory and not helpful in deciding positively the primary origin of the so-called Krukenberg tumor of the ovary.

In 1902 Schenk[2] presented a case, with autopsy, which showed a tumor of the ovary with similar gross and microscopic appearance, with metastases in the abdominal lymphnodes, but without a stomach tumor. He found no other focus of origin for his tumor and he thought that it was a primary tumor of the ovary. He expressed the opinion that such primary tumors are rare in the ovary; indeed he accepts only Krukenberg's first case and his own as true primary tumors of the ovary. He gives no explanation as to the origin of the peculiar cells. Sternberg[3] and Orthmann[4] have described cases which they considered should be classified as Krukenberg tumors. Fischer[5] also described two such cases. These authors agree with Krukenberg as to the primary origin of these tumors, but in no case have they given any explanation or decided definitely as to the origin of the tumor cells.

The conception of the primary origin of these tumors in the ovary is widely disputed. Glockner,[6] in 1904, collected eighteen cases of ovarian tumor, three of which showed a structure similar to that of Krukenberg's, but also found in each case a pyloric carcinoma which he considered to be primary. Wagner[7] reported a case of carcinomatous ulcer of the stomach with tumors of the ovaries which he considered secondary. Schlagenhaufer[8] reported four tumors showing primary foci in the stomach, combined with ovarian tumors showing the Krukenberg histological type. He emphasized the fact that, although there may be true primary Krukenberg tumors of the ovary, that metastases of gastric origin may take on this peculiar structure in the ovary. Kaufman,[9] in his text book, believes that the majority of these tumors are metastatic. Burdinsky,[10] in 1908, described a case of Krukenberg tumor of the ovary associated with a carcinomatous ulcer of the stomach, and considers this case a further argument in favor of the secondary origin of such tumors. Hussy[11] described a case of carcinoma of the stomach in which there were definitely formed acini in the ovarian tumor. This case, therefore, seems to us to have no bearing, on the nature of the tumors under discussion. Cohn[12], in studying four cases, has concluded that they are all secondary in the ovary.

The most recent report (and the only one found in the American literature) is one by Outerbridge[13] of Philadelphia; he reports a case of tumor of the ovary. The description and photographs of the sections of the ovary closely resemble Krukenberg's, and he classes the case as that of a Krukenberg tumor; he states that they are rare but that they may occur primarily in the ovary; he also makes the statement that any tumor of the ovary may undergo myxomatous change, not only in the ground substance, but in the cells.

A review of the literature is of little help in deciding whether or not such tumors do ever occur as primary in the ovary. In many of the cases reported, no autopsy was performed. In our case it would have been difficult to exclude the primary ovarian origin of the tumor with a mere examination of the ovaries. The case of Schenk and Krukenberg's first case are of most particular value and one is led to conclude that these two cases may have been primary in the ovary. But we all know how difficult it is to decide whether there is not a primary tumor in some part of the intestinal tract without thorough microscopic examination. In Krukenberg's first case he leaves us in doubt as to the condition of the stomach mucosa. Outerbridge explains that at operation the stomach was palpated and found normal; we do not believe that it is possible to decide that there is no tumor change in the stomach mucosa simply by palpation.

Dr. Symmers of Bellevue Medical College has very kindly lent me a section of an ovarian tumor removed at operation; the history of his case is similar to ours, but not complicated with pregnancy. The sections studied showed the signet ring cells, as in our case, but there is considerably more fibrous tissue stroma present. (Further observation of the case was impossible, patient leaving the hospital after operation).

There has been considerable discussion as to the paths of dissemination followed by the tumors, by Pfannenstiel[14] and others. In Krukenberg's first case the lymphnodes were infiltrated, according to him, by way of the lymphatics. Kraus[15] examined a series of ovarian carcinoma and found that the growth always appeared earliest at the periphery of the organ; he concludes that there was a direct invasion through the germinal epithelium by wandering tumor cells. Two of his cases resembled Krukenberg's tumors in histology. Stickel[16] doubts this method of direct invasion and considers metastases to occur by way of the lymphatics. Various other authors have advocated the latter theory. (In our case, although the lumbar and peripancreatic nodes were slightly enlarged, there was no further evidence of tumor infiltration, and one of the pelvic nodes showed on section no evidence of tumor growth). Stauder[17], in the study of twenty ovarian tumors, found three tumors similar to Krukenberg's; one of these cases he considers to be a mixed tumor with areas resembling carcinoma, with other areas resembling sarcoma and myxoma. The second was associated with carcinoma of the stomach, and he considers the ovarian tumor to be secondary. He does not state whether the pyloric tumor showed mucoid change in the cells or not. In his third case he described undoubtedly a sarcoma, and thinks that the signet cells are derived from the connecting tissue stroma of the ovary, and agrees with the suggestion of Krukenberg in this respect. In his case, however, he had no autopsy and so, I think, one can place very little value on this case. Anann[18] reported eighteen secondary ovarian carcinomas, four of which were like Krukenberg's. Here and there the tumor cells are single, lying in a connective tissue stroma; in other places they appear in cords. This is indeed very similar to our case. He suggests that the ovarian connective tissue undergoes a definite proliferation, due to the irritation of the tumor cells. He does not say whether such a proliferation occurred in the primary focus. In our case I find that it does occur in the stomach tumor.

Rosthorn[19] states that most of these tumors are secondary, but he is convinced that some are primary. He reports a case of fibro-sarcoma with nodules in the skin, lymphnodes, abdomen the thorax, with his lateral ovarian tumor. The latter on section showed a structure similar to Krukenberg's tumor. He considers the primary focus is in the ovary and classes the tumor as a true sarcoma of the ovary, with mucoid changes in the cells. Sternberg[20] reported a case (as an endothelioma of the bone marrow) in which the bone marrow was shot with tumor nodules. The ovaries were sclerotic and without tumor infiltration. The cells showed a distinct signet ring formation, as do the Krukenberg tumors.

Rosthorn's and Sternberg's cases prove that tumor cells of a mesenchymal origin may undergo intra-cellular mucoid degeneration as well as those of epithelial origin. These statements do not, however, help us to decide the epithelial origin of these tumors.

Conclusion: In carefully comparing the various stages of the tumor nodules in the stomach and cervix of our case, it is seen that the central portion of the nodule shows the same structure as does all the portions of the right ovary. The periphery of the nodules, however, is slightly different; in the central portion we have various transitions, from the small cells with eosinophilic protoplasm up to the large signet ring cells showing marked mucoid degeneration; in the periphery of the nodules none of the cells show mucoid degeneration; they occur in cords rather than singly, as in the central portion of the nodule; their nuclei stain very deeply with hematoxylin and they appear to be actively proliferating.

From this it would appear that the larger the tumor nodule the more mucoid degeneration there is, and the central or older portion shows alone this change. In the enlarged and completely involved right ovary the structure is the same throughout. The increased intercellular connective tissue present around the signet ring cells, I would suggest, may be a sort of pseudo-sarcomatous change of the ovarian stroma, which is seen only in the older parts of the nodules and elsewhere, namely, cervix, etc. This intercellular fibril formation we maintain is coincident with and has definite relation to the onset of mucoid change in the tumor or parènchymal cell. Although no direct relation of the tumor cells to the stomach mucosa can be made out, I consider, for the reasons advanced above, that we have a primary medullary carcinoma of the stomach with the older parts of tumor showing pseudo-sarcomatous changes and mucoid degeneration of the cells, and that the ovarian tumor is secondary to the gastric carcinoma. The term Krukenberg should alone be applied to the microscopic appearance of a tumor and should not be used to designate a distinct type of primary ovarian tumor.

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Discussion.

Dr. F. C. Wood said that he had seen four or five of these Krukenberg tumors of the ovary, all with characteristic morphology, and in all, the primary tumor was in the stomach or gall-bladder. His personal belief was that ovarian tumors of this type were always secondary, arising from a malignant growth in the stomach, gall-bladder, or intestine. In this connection it was remarkable how frequently there was ovarian involvement in carcinoma of other organs. It was not at all an uncommon occurrence in a case of carcinoma of the breast to find the ovary perfectly normal on gross inspection, and yet on making serial sections to discover nodules of undoubted carcinoma in the lymph spaces.

Dr. MacCallum thought that it was rather absurd to name these tumors after Krukenberg, since his diagnosis in his own case was obviously wrong. He had seen several such tumors primary in the stomach with widespread metastases which were composed of loosely arranged cells, each one containing a droplet of a colloid substance.

A CASE OF OSTEITIS DEFORMANS.

V. H. NORRIE, M.D., AND GUY WALLACE, M.D.

The case of Paget's disease is one from Dr. Van Horne Norrie's service at Bellevue Hospital. The patient was admitted November 4th, 1911, dying seventeen days later, and presented the essential manifestations of this disease.

The clinical history is very meagre. The man had been a heavy drinker and smoker; gave a history of chancre, without secondaries; had gonorrhea four times; was a veteran of the Civil War, and during the past twenty years had occupied a position as salesman; during the last two years he had been living on his pension. The patient came to the hospital because he was becoming weaker and was unable to take care of himself. A diagnosis of Paget's Disease was made from the massive head. There was but a slight bowing of the right femur, the hands and feet being normal. There was an indistinct history of muscular rheumatism during the previous year. The patient stated that when fifty years of age he wore a No. 7 hat, and that practically every four years since that time he required a larger one. His picture in uniform, taken at the time of the war, shows no enlargement of the face or head. This cranial enlargement, apart from the sensation of weight, caused him no discomfort.

The chief complaints on admission were, a dull aching pain in the back, weakness, and headache. During his stay in the hospital he developed flaccid paralysis of the left arm, with flattening of the left side of the face, and deviation of the tongue to the left. The radials and temporal arteries were extremely prominent, being practically converted into tortuous pipe-stems. The Wassermann reaction was negative. Broncho pneumonia supervened and, after having been in coma with stertorous respiration for two days, he died.

The autopsy was performed by Dr. Charles Norris the following day and the anatomical diagnosis was as follows:

Cerebral hemorrhage.

Paget's disease.

Chronic and acute pachymeningitis hemorrhagica fibrinosa.

Marked pial oedema.

Extreme arterio sclerosis of cerebral and coronary arteries.

Chronic emphysema and bronchitis.

Lobular pneumonia.

Acute localized fibrino-purulent pleuritis, left.

Acute fibrinous pleurisy, right.

Slight chronic interstitial and acute parenchymatous nephritis.

Enlarged prostate.

Hypertrophy of the lingual follicles.

Body is that of an old man 70 years of age, 5 feet 6 inches in height. There is considerable emaciation of the extremities and trunk. Thorax is moderately long, conformation normal. There is slight bowing of the legs. The knee joints are of normal conformation. The feet, toes, hands and fingers are normal. Breadth of hand 8 cm. The wrist, elbow, shoulder joints and vertebral column are normal. There is abundant dark hair over the chest; the pubae are abundant, masculine in type; there is considerable perineal hair; small amount of hair over thighs, axillary hair abundant. The hair partly gray, is abundant on the sides and scanty over the top of the head; eyebrows are dark and moderately thick; long grayish beard and moustache. The costal cartilages are of normal breadth. The first costal cartilage is calcified, the other cartilage being slightly greenish yellow on section with only a few calcific foci. The ribs are fragile. Intercostal spaces, ribs and cartilages are of normal breadth. Marrow of the ribs is abundant and dark red in color. The liver extends about a hand's breadth below the costal arch. Diaphragm is at the fourth space right and left.

Head: Head is very large and heavy, the face being normal in size. The temporal ridges are large and prominent; the temporal muscle is broad but thin. Tissues of the scalp are thin, as if stretched. The scalp peels readily. The pericranium strips readily. The external surface of the bone is everywhere slightly roughened, hyperaemic and irregular. The parietal foramina are very large and deep; similar accessory foramina are present. The surface is irregularly mottled with pale yellowish areas and reddish areas of hyperaemia. The sutures are everywhere obliterated. Conformation of the calvarium is somewhat irregular, but the symmetry of the skull, as a whole, is maintained. The increase in size of the skull is symmetrical, the calvarium being greatly thickened. The dimensions of the skull following removal of the scalp, were as follows:

Greatest circumference	65.5	cm.
" diam. ant. post	23	"
Bi-parietal	18	"
Bi-malar	13.3	"
Naso-mental	14.2	"
Mento-coronal (length from the chin to the top of skull)	26.5	"
Occipito-frontal	22	"
From zygoma to top of calvarium	12.7	"
Length of the nose	6.5	"
Distance from angle of jaw to symphysis menti	6	"
Anterior fossa, greatest breadth (internally)	10.5	"
Anterior fossa, ant.-post	6.3	"
Middle fossa, breadth	14.8	"
" " , ant.-post	5	"
Breadth of occipital fossa	12.5	"

The forehead is massive. The wings of the sphenoid are not thickened. The infundibulum of the pituitary is long and reddish in color. The Foramen Magnum is funnel-shaped, 2 cm. in breadth. The Clivus Blumenbachii is approximately 5.6 cm. in length 4.4 cm. in breadth. The pituitary gland measures 18 cm. by 12 mm. by 3 mm. Its right lobe is hemorrhagic, The gland is pale yellowish in color and rather firm.

The middle ears are normal. The sphenoidal sinuses are large. The mucous membrane is normal. The dura is adherent, especially on the right side, where it tears on stripping. It is everywhere thickened and the inner surface shows an extensive hemorrhagic membrane formation over the cerebral convexities. The pia is markedly oedematous and the Pachionian granulations are not prominent. A number of small opaque foci, the largest 2 to 3 mm. in diameter, are found in the pia over the vortex, near the longitudinal fissure. There is a considerable amount of blood stained fluid at the base. The brain, after the ventricles were opened, weighs 1440 gm. On the superior surface of the cerebellum there is fresh, reddish blood clot, and there is a considerable hemorrhagic infiltration in the pial meshes along the posterior border of the right lobe of the cerebellum. The vertebrals are markedly sclerotic. The basilar artery is very large, extremely sclerotic, with intense yellowish patches. The arteries of the Circle of Willis and the cerebral arteries are markedly sclerotic. The smaller vessels show extensive nodular sclerosis. The left lateral ventricle is filled with blood stained fluid. The right lateral ventricle containing reddish blood clot. There is an extensive hemorrhagic softening and infiltration involving the posterior and superior half of the lenticular nucleus, which extends into the optic thalamus and the adjacent wall of the third ventricle. The velum interpositum is infiltrated with blood and does not appear to be thickened. Otherwise the cross sections of the brain reveal no gross lesions.

The pineal gland measures 7 to 8 mm. laterally by 5.6 ant. post. The sella turcica is 28 mm. in breadth by 18 mm. ant. post. The clinoid precesses are enlarged. The calvarium is soft, sawing through readily. The thickness of the occipital bone is 2 cm., that of the frontal bone 1.5 cm. The diploe are noticeable only in the occipital bone.

Lungs: The pleural cavities are free from fluid or adhesions with the exception that the left apex is slightly adherent. The pleurae of both lungs feel sticky. The right lung is slightly emphysematous, the surface being roughened and irregularly mottled. An extra fissure, 2″ in length by 1″ in depth, is present in the lower lobe. The larger and smaller bronchi contain mucopurulent exudate and the mucous membrane is markedly congested. Section shows an extensive lobular pneumonia involving all lobes and more marked posteriorly. The left lung is rather voluminous; it does not feel heavy; is well aerated; the surface is smooth and on section shows nothing abnormal, with the exception of slight congestion. The pulmonary vessels are normal except for a few areas of intimal thickening. Bronchial lymphnodes are small and anthracotic. There is no evidence of a tuberculous process either in the lungs or in the lymphnodes.

Heart: The pericardium is normal and contains a small amount of clear fluid. The heart is normal in size, the apex being formed by the left ventricle. The vessels are slightly tortuous and show a few areas of nodular sclerosis. The right auricle is normal. Fossa ovalis is normal in size. The foramen ovale is patent. Endocardium is silghtly opaque. Tricuspid valve measures 13 cm. and is normal. There is no hypertrophy or dilatation on the right ventricle. The mitral ring shows a slight narrowing, the aortic segment being contracted and calcified at its base. The wall of the left ventricle measures 25 mm. in thickness; the musculature is pale brownish red in color and on section shows numerous small areas of fibrosis. The aortic cusps are slightly thickened and calcified at the line of their attachment; the line of closure is, however, normal. The portion of the aorta below the first part of the arch is the seat of a slight patchy sclerosis. The arch, thoracic and upper part of the abdominal aorta being normal. The branches of the abdominal aorta are only slightly sclerotic. The lower half of the abdominal aorta and the iliacs are somewhat broad but show only a slight sclerosis.

Spleen: Is small, rather firm, weighs 100 gm. and measures 10½ x 4½ x 4 cm. On section it is congested and shows a slight increase in interstitial tissue.

Pancreas: Is about normal in size; lobulations are normal.

Liver: Weighs about 1600 gm. The serosa is normal and pale brownish in color. The surface is smooth and on section the lobulations are indistinct, otherwise normal.

Gall Bladder: Is long and contains numerous facetted stones, there is a very large number present. Common bile duct normal. Patency was not tested.

Adrenals: Left adrenal measures 5½ cm. in length by 2½ cm. in breadth. The right adrenal measures 6 x 4 cm. The organs are somewhat firm. The cortex is pale yellowish in color and measures 2 to 3 mm. in breadth. The medulla is dark red in color and shows a few patches of glistening tissue.

Kidneys: The right kidney 120 gm., left 160 gm. They are somewhat firm, apparently normal in size. The capsules are adherent in a few places. The surface is slightly granular. Signs of fetal lobulations persist. There are a few superficial scars on surface. The cortex is thickened and pale, the markings are distinct. The pelves, ureters and urinary bladder are normal. The prostrate is large; otherwise normal. The testicles and epididymes are normal in size and appearance; there is a small hydrocele on left side.

Oesophagus: Shows a few distended veins in its upper half; otherwise normal.

Stomach: The mucous membrane is congested. There is a small, whitish area situated beneath the cardia of the mucous membrane (Lymphangioma).

Intestines: Small and large intestines contain a small amount of gas and hard fecal material. Appendix is normal. In the coecum there is a small, reddish focus, 3 x 4 mm., which is freely moveable. There are several pale yellowish areas in the wall of the jejunum (Lymphangiomata). The mesentery is somewhat fatty. The lymph nodes are abundant but small.

Organs of Throat and Neck: The tongue is apparently normal in size. The lingual follicles are increased in size and number. There are a number of pale, elevated areas at the back and sides of the tongue, which on section show a milky fluid. The pharynx and larnyx are normal. The tonsils are enlarged, the right showing a number of depressions filled with exudate.

The thyroid gland is somewhat symmetrically enlarged and pale reddish on section. The organ was not weighed. The parathyroid glands were removed.

The following measurements were made of the pelvis:

Intercristal	27	cm.
Interspinous	23.2	"
Internal conjugate	11.2	"
From the greater trochanter to plane of surface of foot	34.5″	
" ant. sup. spine to plane of surface of foot	37.4″	
Ant. sup. spine to bottom of external condyle of femur	19″	

The right knee joint is normal as to its articular surface and mucous membrane. The right femur is bowed. It is broad in its lower half and measures 18 cm. immediately above the condyles. On section the cortex measures 1 cm. in diameter. The diameter of the bone is 3.1 cm. The cortex of the left femur measures 6 mm. The diameter of the whole bone is 3.1 cm., right and left being of the same diameter. At a place above the middle of the right tibia, the thickness of the cortex is 1 cm. The bone is very firm, almost ebony-like. Vertebrae and marrow everywhere normal.

Ribs:. The marrow is red in color and normal in amount.

One of the earliest terms used in referring to diseases of bones is rickets. This term was used to include all diseases in which extensive bone changes occurred. Since then, groups of cases have been separated, such as Infantile Rickets, Achondroplasia, etc. The term Osteitis Deformans has long been used in connection with various diseases, which resulted in deformity of the affected bones. This term included constitutional diseases, fractures, and congenital deformities. The term was first used by Czerny in 1873 to describe a case of spontaneous curvature of the lower limbs. (This was in all probability a case of Osteomalacia.)

Sir James Paget who, in 1876, made use of the term Osteitis Deformans, in describing the condition which now bears his name, remarks in his original article: "Holding then the disease to be an inflammation of the bone, I would suggest that, for brief reference and for the present, it may be called after its most striking character, osteitis deformans. A better name may be given when more is known of it."

Since that time various names have been applied to conditions apparently analogous to that described by Paget. To Paget's[1] original description, which appeared in the Medico-Chirurgical Transactions, 1876, little of note has been added. As he described it, the disease begins in middle life or later, progressing slowly during a period of many years, and causing no disturbances other than those due to mechanical changes in the diseased bones, those most often involved being the long bones of the lower extremitiy, the cranium, spine and clavicles. These enlarge and soften, and, owing to the pressure of the body and muscular traction, become curved and misshapen so that the statue steadily decreases. In a later communication, he states that there is not any clear evidence of general disturbance of health. In all cases, death has ensued through some coincident, not evidently associating disease, which has been aggravated by the condition of the bones, only in so far as they may have diminished the range of breathing and the general muscular activity. Paget correctly interpreted the condition as being a chronic inflammatory process.

Considered as a rather rare condition, Clopton, in 1906, collected seventy-five cases from the literature. Higbee[3] and Ellis, in recording a case in the *Journal of Medical Research*, 1911, state that the number has been increased to 158 cases, 33 of which were noted in this country. The relative increase during the past few years points to one of two things—that the disease is becoming more prevalent or is more often recognized as such.

Numerous names have been applied to this condition, which illustrates the views of different authors, according to their interpretation of the process:

Osteitis deformans (Paget).
Pseudo-rachitis senilis.
Osteo-malacia chronica deformans hypertrophica.
Ostéite ossifiante diffuse (Lancereaux).

Osteolysis (Lobstein).
Hypertrophie spongieuse des os.
Craniosclérose.
Hyperostose généralisée.
Ostéite condensante.
Ostéomalacie hypertrophique benigne (Vincent).
Pseudorachitisme senile.
Osteomyelite fibreuse.
Sclérose osseuse hypertrophique.

In reference to the etiology, little is known. In spite of the many theories that have been advanced, there is no generally accepted etiological factor. The most important are of interest, in that they tend to show the wide divergence of opinion.

Lesions of the nervous system, hereditary lues, arteriosclerosis, metabolic changes, and disturbances in secretion, particularly of the thyroparathyroid group, testicular, and suprarenal glands, have all been suggested as etiological factors.

Prince[4] suggests, that it is not inconceivable that as degeneration of the anterior cornua may cause myopathies without other symptoms; so lesions of other special cell groups may cause osteopathies without other spinal symptoms. Curcio[5] also suggests the possibility of a special trophic center in the gray matter of the spinal cord because the manifestations of the disease are usually symmetrical.

Syphilis: Some observers, particularly, Lannelongue[6], regard the disease as a manifestation of congenital syphilis or a paraluetic condition, asserting that improvement has been noticed following the administration of mixed treatment. Fournier[7] agrees with Lannelongue and mentions the case of two brothers, one of whom presented a typical clinical picture of Paget's disease, the other showing marked evidence of congenital syphilis. He later speaks of the disease as a paraluetic condition, to be classed with tabes dorsalis, general paresis, etc. Von Recklinghausen[8] considers that the disease is not specific. Robin[9] endeavored to differentiate Paget's from the luetic osteitis by comparison of the chemical composition of the bones, but his results are of little value at present, as only one case was analyzed. Weber[10] says that the osteitis deformans of congenital syphilis and Paget's may be differentiated as follows: 1. The youthful age of the patient in cases of congenital syphilis; 2. The relative absence of pain, which is almost constant in Paget's; 3. The favorable results obtained in syphilitic cases with proper treatment; 4. In syphilitic cases the tibiae are most severely affected, in Paget's disease the femora; 5. The presence of irregular bosses in congenital syphilis; 6. There is no evidence of any tendency for malignant tumors to supervene in the bones of syphilitic cases, as there is in Paget's.

Heredity: Several instances are recorded in which members of the same family have been afflicted with this disease. Chauffard[11] mentions mother and daughter; Smith[12], a father and son; Berger[13], a mother and son. Paget, however, in reviewing 27 cases, remarked on the entire absence of any such history.

Occupation: Oettinger[14] and Agasse Lafont noted that several cases had occurred among those whose occupation, such as bleachers, tanners and hatters, subjected them to the action of certain acids. They considered it possible that the chemicals may have some action on the osseous structure.

Arterio-Sclerosis: This condition is present so frequently that it may be considered almost constant. Not a few, particularly Béclère[15], have considered that the interference with nutrition, resultant upon the sclerosis of the nutrient arteries of the bones affected, may have some etiological bearing.

Heitz[16] and Hudelo speak of a woman 75 years of age, in which the skull was unchanged but whose femora and other bones presented lesions of Paget's disease. Arterio-sclerosis was not uniform. In this instance the arteries of the brain, skull and neck were normal, while those of the remaining viscera showed marked sclerosis, even to obliteration.

Interference with the function of the glands, and disturbance in the internal secretions has been considered. Our case is interesting in the entire absence of any change in the glands of internal secretion, so far as determined. The lesions of the nervous system described in cases of Paget's disease should be accepted with considerable reserve. We believe this because of the pronounced arterio-sclerosis almost constantly associated with the disease, and because of the senile changes so frequent in brain and spinal cord, in old age. On account of the frequent association of arterio-sclerosis with the disease, it seems reasonable to suppose that it may act as a causative factor.

It is of interest to note that Max Koch[17], before the German Pathological Society, demonstrated a case of Leontiasis ossium, and showed that the microscopical picture was similar to that occurring in Paget's disease. He therefore considers them identical.

We are unable to explain in detail how the vascular changes could so markedly alter the osseous tissues. That the process is evidently not always a generalized one leads us to suppose, that more consideration should be given to local disturbances, than to a general disturbance involving the osseous system as a whole.

Perhaps, as Higbee and Ellis state, accurate studies of the metabolism offer the most hopeful means of arriving at the proper solution of this question. Although we favor the idea that it is a local condition and not a systematic one, we realize that there must be some other causative factor present, for the reason that so many cases of marked cerebral arterio-sclerosis show no changes in the osseous system.

Microscopic examination of sections from our case show as follows:

Occiput; Section taken from the occiput—the outer table is formed of a thin layer of dense bone; there is little differentiation in structure of the bone. The inner table is very thin; the marrow spaces are large and everywhere filled with connective tissue composed of a homogeneous stroma and connective tissue cells with small spindle-shaped nuclei. The vessels are large; there is no proliferation of their endothelial cells. In places the connective tissue is more fibrous in character; the osseous trabeculae are large; there is well developed concentric lamellar formation; the bone cells are small; there are few Howships lacunae and only in places are there osteoblasts. To be brief, the process may be described as an osteitis or osteomyelitis fibrosa; the trabeculae are large, well connected with each other, and there is everywhere evidence of a formative osteitis. The bone was extremely difficult to decalcify, and there is every evidence that there was no marked halisteresis.

Tibia: Section taken from the cortex of the tibia, which was thickened as above mentioned, shows very dense bone.

Right Femur: The cortex is formed of rather dense bone with large vascular marrow spaces, showing an osteogenic connective tissue very similar to that found in the occiput. Only a few giant cells are seen. The periosteum is thickened and fibrous; the inner layer is cellular.

Left Femur: The section taken at a level corresponding to that of the right femur is normal.

Vertebrae: Shows normal lymphatic marrow, in places quite fatty.

Ribs: The marrow spaces are very wide; trabeculae long and narrow.

Clavicle: Shows no noteworthy changes.

The gross lesions and the microscopic sections indicate that there has been an extensive formative osteitis of the calvarium, corresponding to what Von Recklinghausen has described as an osteitis fibrosa.

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DEMONSTRATION OF THE LESIONS PRODUCED IN THE APPENDIX BY OXYURIS AND TRICHOCEPHALUS.

RUSSEL I. CECIL, M.D.

Dr. Cecil presented a series of lantern slides showing various phases of the invasion of the appendix by oxyuris vermicularis and trichocephalus dispar. He divided the cases into four groups as follows:

1. Those cases in which the appendix was the seat of catarrhal inflammation, but in which the worms had apparently remained inactive in the lumen of the appendix.
2. The cases in which the parasites had punctured or invaded the mucous membrane.
3. The cases in which the oxyuris had not only punctured the mucosa, but had produced more or less extensive ulceration of it.
4. The cases in which the appendix was gangrenous. In these no characteristic parasitic lesions could be demonstrated.

Dr. Cecil also demonstrated some healing oxyuris lesions—one of them consisting of a hyaline parasite completely encapsulated by fibrous tissue.

The trichocephalus lesions were shown to differ slightly from the oxyuris lesions. In the former the parasite tunnels along immediately beneath the epithelium, while in the latter the worm usually burrows into a lymph follicle.

In conclusion, Dr. Cecil said that in his series of 129 cases of appendicitis in children, 15% of them had been found to be associated with parasites, and that of these 70% showed specific parasitic lesions.

A CASE OF DISSECTING ANEURISM AND AORTITIS DISSECANS.

J. GARDNER HOPKINS, M.D.

The specimen was obtained at autopsy on the body of a woman, fifty-four years of age. The clinical history was of little interest. The patient was admitted to the hospital with bronchopneumonia, which followed a favorable course. Death was due to rupture of an aneurism into the left pleural cavity. At autopsy the hemorrhage was found to come from a large false aneurism lying between the pleura and the diaphragm. This opened into the aorta by a large gap measuring 5 cm. vertically by 1 cm. antero-posteriorly. The aneurismal sac extended 11 cm. from the aorta nearly to the lateral chest wall. The remnants of the arterial sac were found in the wall near the aorta, but elsewhere the sac was lined with fibrous tissue and nearly filled with dense lamellated thrombus. There was also a fusiform dilatation of the ascending portion of the aortic arch.

The lesion of chief interest, however, was a dissecting aneurism which lay in the left wall of the thoracic aorta. It was 13 cm. in length and 2 cm. in diameter. It communicated with the lumen of the aorta by a small opening, 11 cm. below the left subclavian. This opening just admitted a probe. The sac extended about 2 cm. above this point, ending blindly, and at an equal distance below was bifurcated, one neck communicating with the neck of the false aneurism previously mentioned. The other branch ended blindly about the level of the celiac axis. This branch was filled with a laminated thrombus. The wall of the dissecting aneurism was thick and nodular, in places reaching a thickness of 1.4 cm. The tissue was firm and fibrous, the lining for the most part smooth, but showing some areas of atheroma and calcification. The aorta showed extreme sclerosis. There were deep ulcerations of the intima separated by calcareous plaques with sharp edges. These changes were most marked in the abdominal aorta, but involved the entire vessel. The vessel wall was stiff and on section clefts were found in the substance. These were apparently preformed, though it is possible they resulted from trauma in section. If they were artifacts the tendency to form such clefts under slight stress was very marked. The other organs showed nothing of note.

Sections through the dissecting aneurism showed that it lay in the media of aorta inside the external elastic lamella. The elastic fibers of the media were fragmented and partly replaced by hyalin connective tissue infiltrated with round cells. The adventitia was very thick. The walls of the vasae vasorum were thickened by fibrous tissue and the endothelial cells were swollen. Some of the veins were entirely occluded by masses of leucocytes. The vessels were surrounded by collections of plasma cells and lymphocytes. Foci of these round cells were found elsewhere in the adventitia, but none of them contained giant cells or showed central necrosis. Spirochaetae could not be demonstrated in them by the Levaditi method. The picture was extremely suggestive of a gummatous process, but did not warrant an absolute diagnosis of syphilis. The intima of the aorta was thickened by atheromatous masses. Sections also showed areas of calcification in the intima. The inner wall of the dissecting aneurism showed similar atheromatous changes. The lumen was lined in part with a layer of flat cells resembling endothelium. Similar lesions were found in the abdominal aorta. The clefts in the wall found on cutting the vessels seemed to lie in the media inside the elastica externa, a position corresponding to that of the dissecting aneurism. The clefts were traversed diagonally by strands of unruptured fibers. Smaller clefts were found elsewhere in the media.

Changes of this type have been described from time to time in cases of dissecting aneurism, and Rokitansky (*Lehrb. d. path. Anatomie,* 3d ed. II., p. 344) spoke of the possibility of their being the underlying cause of this peculiar lesion. He suggested two possible explanations of the lesion: first, that the freeing of the adventitia was primary, and the rupture of the media and intima secondary, due to loss of the support normally given by the adventitia; second, that the rupture might be primary and the freeing of the adventitia secondary, if the disease impaired the elasticity of the media more than that of the adventitia.

Babes and Mironescu (*Beit. d. allg. Path. u. path. Anatomie*, 1910, xlviii, 221) have described a case of dissecting aneurism in which they found that the whole aorta had a tendency to split easily when cut, or contained preformed clefts in the wall. On section they found areas of hyaline degeneration in the intima and media and foci of round cell infiltration. They regarded this condition of the vessel, which they described as aortitis dissecans, to be the underlying cause of the dissecting aneurism.

A CASE OF OVARIAN PREGNANCY AND ONE OF TUBO-OVARIAN PREGNANCY.

J. GARDNER HOPKINS, M.D.

The specimen was obtained at operation on a patient of Dr. E. B. Cragin's at the Sloane Hospital for Women. The patient was a married woman, thirty-nine years of age, who had five children, the youngest being three years of age, and two miscarriages, the last two years before operation. The last menstruation occurred two months before operation. Without prodromal symptoms she was seized with sharp cramp-like pains in the lower portion of the abdomen, which lessened somewhat in intensity but continued until operation three days later. She had no bleeding and practically no other symptoms; her temperature was normal. Physical examination was negative except for tenderness, most marked on the left side. At operation two tumor masses were seen in the region of the left broad ligament. The tube on this side was normal; anterior to it was a thin-walled cyst, evidently parovarian, and posteriorly in the region of the ovary, a deep red mass adherent to the posterior wall of the Cul de Sac, which ruptured on removal, freeing a considerable mass of blood clot. The right ovary contained a few small cysts. The pelvic viscera were otherwise normal.

The specimen consisted of the left tube and the two cystic masses mentioned above.

The tube was 6 cm. long, 1 cm. diameter at the ampulla, very slightly convoluted, and not appreciably thickened. The fimbriated extremity was free and the fimbriae extended down a short distance over the surface of the parovarian cyst. The tube was not adherent to the ovary.

The parovarian cyst measured 6.5 x 4.5 x 5 cm. The wall was less than half a millimeter in thickness, and smooth, and showed two overlying systems of blood vessels. It was filled with clear fluid.

The ovarian sac was widely open when received. The blood clot which was found in it measured 6 x 5 x 3 cm. and was firm in consistence. The sac wall varied from 3 to 1 mm. in thickness, was opaque, and contained a few small cysts flattened out. The inner surface was rough and irregular and portions of the blood clot remained adherent to the wall. The sac was not attached to the tube, but was bound to the parovarian sac by a thick fibrous pedicle. The ovarian ligament was not definitely identified.

Sections were taken from all three structures. The tube appeared normal, showing no evidences of pregnancy.

The cyst had a thin fibrous wall and was lined by high cylindrical epithelium. The blood clot showed a few much degenerated chorionic villi. Other villi were found in portions of clot adherent to the sac. The remains of the fetus were not found. The sac wall showed typical ovarian stroma, the remains of a corpus fibrosum and of a few young follicles. Ovarian tissue was found in several portions of the wall. The lining of the sac was made up of dense fibrous tissue, poor in nuclei undergoing hyaline change. Large masses of this tissue were found in portions of the wall. It did not apparently represent an ovarian cyst.

This seems a definite case of ovarian pregnancy. While the condition has aroused considerable interest on account of its rarity, it was described by Erceres in 1614, but the diagnosis in the early reported cases was not definitely established. In order to make a definite diagnosis it is generally considered that the specimen fulfil the requirements laid down by Spiegelburg in 1878: 1, the tube must be intact; 2, the fetal sac must be in position in the ovary; 3, the ovary must be connected with the uterus by the ovarian ligament; 4, ovarian tissue must be found in the sac wall. Williams has added the requirement that ovarian tissue must be found in several portions of the sac wall, and Norris that the tube must show no microscopical evidences of pregnancy. This case fulfils all the requirements except identification of the ovarian ligament.

There are probably many unreported cases of ovarian pregnancy and many reported cases may well have been true ovarian pregnancies, although the reports are too incomplete to establish the diagnosis. In 1909 Norris collected nineteen positive cases. I have been able to find three cases reported since then, all apparently positive; one reported by Lea in the *Journal of Obstetrics and Gynecology* for the British Empire in 1910; one by Kubin, published in the *American Journal of Obstetrics* for 1911; and the third by Young and Rhea in the *Boston Medical and Surgical Journal* for 1911.

The diagnosis is most easily made in early cases, of which this is an example. The diagnosis was, however, definitely established in a case of Ludwig's which ran to term, one twin being delivered from the uterus and another living twin from the ovarian pregnancy by laparotomy

The symptoms are inconstant; there is frequently no bleeding, and in one case the patient had normal menstruation a few days before operation.

Much more common than true ovarian pregnancy are the so-called tubo-ovarian pregnancies in which the sac well is composed partly of tube, partly of ovary. These may originate in one or two ways, either by rupture of a true ovarian pregnancy, or by rupture or abortion of a tubal pregnancy into a tubo-ovarian cyst. The second specimen is an example of the latter condition.

The clinical history of this case was of little interest. The patient complained of pain in the lower abdomen for the five weeks before operation and of profuse bloody discharge, which was increased by exercise. At operation a hematoma was found occupying the position of the right broad ligament, which ruptured on removal. The fetus was not found. The tube was densely adherent to the sac wall with which the fimbriated extremity was fused. The tube was unruptured, but there was blood clot in the ostium.

The section from the ampulla of the tube, which was filled with blood clot, showed well preserved chorionic villi in the lumen. The wall of the sac resembled in gross, ovarian tissue, and on section showed typical ovarian stroma with numerous follicles and a flattened-out corpus lutem cyst.

It seems fairly clear that this specimen represents the abortion of a tubal pregnancy into a tubo-ovarian cyst. The presence of villi in the tube seems to exclude the possibility that the pregnancy was primarily ovarian.

Discussion.

Dr. James Ewing: Did not Dr. MacCallum present a specimen of ovarian pregnancy before this Society within a year or so? Of course, the careful distinctions between tubal gestation and ovarian gestation are of considerable interest. At the same time, if without requiring all the data, one includes the extra uterine gestations, which are largely ovarian, I think they amount up to a very considerable figure. And as such cases have very much the same significance, I think the impression that general ovarian pregnancy is a rarity is perhaps not well founded.

I have encountered cases which meet the requirements which Dr. Hopkins mentions, in that they were practically completely surrounded by ovarian tissue. But it is probable that many cases which pass as ovarian gestation are, or that border line which Dr. Hopkins so clearly defines.

DEFECTIVE DEVELOPMENT OF THE RIGHT LUNG, DUE TO ANOMALOUS DEVELOPMENT OF THE RIGHT PULMONARY ARTERY AND VEIN, ACCOMPANIED BY DISLOCATION OF THE HEART SIMULATING DEXTROCARDIA.

E. A. PARK, M.D.

The subject of this report is a male child, two and one-half months old, admitted to the New York Foundling Hospital about two weeks before death occurred.

No history previous to admission is known.

The physical examination, in so far as it had bearing on the conditions found at autopsy, is as follows: A poorly nourished child. Color pale. Body normally formed. Chest symmetrical and moves with respiration alike on both sides. Abdomen has normal contour. The pulsation of the heart can be seen on the chest wall to the outer side of the right nipple in the fourth space and is fairly localized. It can be distinctly felt. Percussion shows dulness over a spot about the size of the normal heart situated in the lower part of the front of the right chest, separated from the right sternal margin by about ½ cm. and not well defined above and to the right because of dullness of a somewhat different character. On auscultation the heart sounds are well heard over the front of the right side of the chest, but maximum at its lower part, at about the point of maximum pulsation. The sounds are normal, clear and unaccompanied by murmurs. The action is regular, but rapid. The left side of the chest in both front and back is very resonant, and the breath sounds are very intense and vesicular. Scattered subcrepitant rales are heard at the base behind. Over the normal site of the heart pulmonary resonance and vesicular murmurs are undiminished. Indeed, they both extend across the sternum to a point about 1 to 2 cm. beyond its right border. Over the right side of the chest, excluding that part of it where apparently the heart lies, the percussion note is dull and the breath sounds are feeble, although in no place absent. Many subcrepitant rales, some of them having a consonating quality, are heard, more particularly over the lower parts than above. Fremitus is not obtained. But voice is more intense at the right base behind and in the axilla than on the left side.

The small intestine can be outlined through the thin abdominal wall and moves with respiration. The sigmoid, it is thought, can be felt in its usual situation.

The liver can be plainly felt extending 1 to 2 cm. below the costal margin. Its upper border percusses dull at the fourth interspace. The spleen cannot be felt. Both kidneys can be felt deep in the flanks.

In other respects the examination is normal.

The X-ray picture shows the heart to lie on the right side of the chest, separated 1 cm. from the right border of the sternum, and to be of normal size. The apex is directed to the left. The left lung seems to be entirely normal. The right lung apparently is consolidated in all but its upper part but the shadow of the upper part is not clear.

The clinical diagnosis was Lobular Pneumonia. Dextrocardia without rotation of the abdominal viscera. Marasmus.

The essential autopsy findings are these: The abdominal cavity presents a normal situs. The liver projects below the right costal margin a distance of ½ cm. The stomach and coils of small intestine are somewhat distended. The spleen lies well back in the left flank. The diaphragm is intact and stands on the right side at the fourth interspace, on the left at the fifth rib. On opening the thorax the entire left side of the chest is occupied by the left lung, which extends also into the right chest about 2 cm. beyond the right border of the sternum. About two-thirds of the thoracic cavity are occupied by the left lung. The heart is seen well over to the right side, presenting by an opening between the lung margins about 3 by 4 cm. The right lung appears anteriorly only as a thin border to the right side of the heart.

On opening the pericardium, which is normal, and exposing the heart to view, the apex is found to be directed to the left and formed by the left ventricle. Its anterior surface is entirely normal, except that the left auricle sends a finger-like process about ½ cm. long forward across the pulmonary artery to rest on it and the adjacent part of the right auricle. The aorta is given off from the left venticle, arches normally and gives its branches in the normal order and size. The pulmonary artery is given off from the right ventricle in normal position and is normally sized. The heart is certainly not enlarged. On further examination it is seen that the pulmonary artery divides normally into a right and left branch, but that the right is very small, not more than one-quarter the size of the left. Moreover, on dissecting clear the left auricle, it is found that two large veins enter it from the left lung, but no other pulmonary vein enters it at all. The right auricle receives inferior and superior vena cava in normal fashion. But no vein from the right lung can be traced to it or to the superior vena cava.

On opening the heart no abnormality is found in its interior.

The left pleural cavity is free from adhesions. As already stated, the left lung is very voluminous and composed of two lobes. Its color is yellowish gray; its pleural surface shining. It crepitates throughout and is normal on section. On examination of its hilus, bronchus, pulmonary and bronchial arteries and the two pulmonary veins can be identified and have normal relations.

The right pleural cavity contains adhesions. The lower half of the right lung is firmly attached to the chest wall. The lung is yet more firmly attached to the diaphragm, from which it is necessary to separate it by sharp dissection. On removal and examination of this lung it is found to be not more than one-half the size of the left and to be composed of three lobes. Its color is dark red; its consistency is firm, through some crepitation is found in its upper portion. To the moment of writing this lung has not been sectioned.

The hilus of this lung shows the cross section of a bronchus about the size of the left, of a thread-like bronchial artery, and a pulmonary artery, which, as already noted, is very small. No pulmonary veins are present at the hilus.

On examination of the under surface of this lung the cut ends of four arteries from 1 to 2 mm. in diameter are seen emerging from its surface. The other cut ends of the arteries are seen on the upper surface of the corresponding part of the diaphragm and can be traced as branches of a greatly enlarged phrenic. The blood supply of this lung, then, is obtained from the minute bronchial, the pulmonary of very small calibre, and the branches of the right phrenic artery piercing the diaphragm to enter its under surface. On separation of the upper and lower lobe of the lung a large vein is seen receiving branches from both lobes. It passes downwards between them to the under surface where its cut end appears. On examination of the upper surface of the diaphragm it could be traced emptying into the inferior vena cava immediately at its point of emergence from the diaphragm. This vein is not the right phrenic vein, for the latter can be identified as a delicate vessel terminating on the under surface of the diaphragm.

The abdominal viscera are essentially normal, with the exception of the liver, the upper surface of which is configured abnormally.

For the preparation of this specimen we are indebted to Dr. Schulte of the Department of Anatomy of the College of Physicians and Surgeons. Dr. Brown, who has been at work on the development of the pulmonary veins affords the following explanation:

The explanation of the anomaly is seen by reference to the embryology of the pulmonary vein. In a very early stage of the embryo of the domestic cat, represented by a length of 4.5 mm., the following condition of the venous system is found. Surrounding the entire length of the gut tube and existing also within its walls is a plexus of veins. This plexus communicates below with the omphalo-mesenteric veins passing in from the yolk sac. At this stage the heart presents an "S" curve which brings the venous chamber to the most cephalic and dorsal aspect of the organ. On either side of the venous chamber of the heart is seen a large afferent channel, the duct of Cuvier. The auricle at this time is a single large chamber, presenting at its cephalo-dorsal angle the opening of the combined ducts of Cuvier forming the sinus venosus.

The plexus of veins around the gut tube above mentioned enters the auricular chamber by two taps, one situated cephalad and one ventrad to the opening of the sinus venosus, the other caudad and dorsad to that opening. At the point where the more cephalic tap leaves the ventral aspect of the gut there is a projection extending caudad which is the Anlage of the lung, and the plexus surrounding this projection, including the tap into the auricle, is the Anlage of the pulmonary system of veins. The tap spoken of as emptying caudad to the sinus venosus represents the future pars hepatica of the adult post cava.

It will be seen from the foregoing that the blood from the lung bud and the adjacent portion of the gut may select one of two routes to gain the auricular portion of the heart; first, directly through the pulmonary vein to the auricle, and secondly, by passage downwards to the level of the post caval tap and entering through it. In the normal development the septum transversum or diaphragm develops between the pulmonary and post-caval tap, and with this development a break takes place in a horizontal direction between the pulmonic venous return above and the post-caval return below, thus causing the blood from the lung to return to the heart by way of the pulmonary vein.

In this anomaly the break between the pulmonic and the post-caval systems has apparently occurred in a longitudinal direction, and the right pulmonary vein instead of passing inward and forward in its normal course to the left auricle, passes downward along the original embryonic communication on the left side, passing through the septum transversum and emptying into the post cava where that channel passes through the diaphragm.

Maud Abbott in her article on "Congenital Anomalies of the Heart," in Osler's System of Medicine, refers to cases of anomalies of the pulmonary veins, in which one or more emptied into the superior vena cava, or into the right auricle. But we have not been able to find a case in which the pulmonary vein emptied into the inferior vena cava.

Eppinger[1] reports a case in which a maldeveloped part of the right lung was supplied by the phrenic artery, which penetrated the diaphragm to accomplish it. But more than four pulmonary veins he found entering the left auricle.

Displacements of the heart, due to defective development of the lungs, are not very infrequent, and when the defective lung is on the right side, may simulate dextro-cardia. The other lung undergoes a compensatory hypertrophy. But such cases are not dextro-cardia.

Dextro-cardia, without situs inversus, has been recently studied by Nagel[2]. His series of six cases, which were proven at autopsy, had certain characteristics in common, one of which was the direction of the apex to the right, shown not to obtain in our case by the X-ray. All six presented defects in pulmonary artery and ventricular septum.

In our case the defective development of the lung seems most likely to be extra-uterine in the time of its occurrence and due to the deficient blood supply from the right pulmonary artery. The phrenic branches represent probably a compensatory means of blood supply. That the defect in development which caused the vein playing the role of pulmonary vein to empty into the inferior cava could also have resulted in an adherence of lung to diaphragm and so have afforded a means of entrance of the phrenic vessels into the lung, seems probable.

What the pleural relations to the phrenic vessels were could not be determined. In Eppinger's case the pleural investment was by a continuation of the ligamentum latum pulmonis. But in the subject of this report adhesions between parietal and visceral pleura about the lower part of the right lung were so extensive as to make such a determination impossible. These adhesions indicated an inflammatory condition in the right lung, probably extra-uterine. Light can be thrown on this by histological study of the right lung.

This case will be reported more fully elsewhere.

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[2] NAGEL: *Deutsches Archiv für Klinische Medizin.* Bd. 96, p. 552, 1909.

AN INFECTIOUS ENDOCARDITIS FOLLOWING MEASLES IN A CHILD AGED TWO AND ONE-HALF YEARS.

E. A. PARK, M.D.

The clinical history of this case is substantially as follows:

Previous to the present illness, the child had been well and had no acute diseases of any kind. The present illness began with an attack of measles, which was part of an epidemic of measles then present at the New York Foundling Hospital. In company with several other children, this child developed Koplik spots, catarrhal symptoms, fever, and a macular eruption which was regarded as being fairly typical. In addition to the house staff, the case was seen by Dr. Rowland G. Freeman and Dr. Matthias Nicol, both of whom concurred in the diagnosis of measles. With the measles the child developed pneumonia and seemed very sick. The eruption differed from that of the other children in that it was slower in reaching its full development and became what was termed "hemorrhagic," although at autopsy no evidence of diffuse hemorrhages into the skin were present. Four or five days after the eruption was first noted, nine days after onset, the temperature, which had been elevated at 103° to 104°, began to assume a septic type, ranging from 105° to normal. The child seemed to be very sick and died about fourteen days after the beginning of the illness. The clinical diagnosis was measles, complicated by broncho-pneumonia.

The autopsy was performed by Dr. Pappenheimer. An abstract of his protocol is as follows:

Anatomical diagnosis.—Acute infective endocarditis of the mitral valve. Lobular pneumonia. Acute hemorrhagic nephritis with infarcts. Infarcts of spleen. Multiple focal necroses of liver. Double suppurative otitis media. Necroses of heart muscle. Petechial hemorrhages of skin and mucous membranes.

External examination. The body is that of a well nourished child weighing about 30 pounds. Length 88 cm. Head circumference 46 cm. Chest measurement 42 cm. Sterno-public measurement 29 cm. Rigor mortis is present in all the extremities. The skin and visible mucous membranes are pale. There are a few dull purplish areas over the upper part of the abdomen, the thighs and the arms. There is marked hypostasis. Over the entire back the skin is desquamating in the form of fine scales.

Examinataion in situ.—The subcutaneous fat measures about 1 cm. over the abdomen. The omentum is free and contains a little fat. It overhangs the somewhat contracted small intestine. The appendix overhangs the pelvic brim in the right iliac fossa and has a short mesentery. There are very numerous hemorrhagic lymph nodes in the mesocolon and in the mesentery itself and along its root. These vary in size from 1 mm. or less, to 2 cm., are brilliant red in color and especially numerous along the attachment of the mesentery to the transverse and descending colons. The diaphragm stands on the right at the 5th interspace, on the left at the 4th rib. The spleen does not reach to the free border of the ribs and lies in the mid-axillary line. The peritoneum is smooth and glistening.

Thorax.—The pleural cavities are free from fluid. There is a single fine fibrous adhesion between the lower border of the left lower lobe and the parietes. The pericardium contains a few cubic centimeters of clear yellowish fluid.

Thymus.—Consists of a rather dense structure. Weight, 4 gm. The tissue about is somewhat oedematous. On section the lobules are rather indistinct and of a grayish yellow color. The glandular substance is atrophic.

Lungs.—The left lung is voluminous, especially the upper lobe, the anterior portion of which is exceedingly pale with emphysematous vesicles. The lower lobe is darker in color but somewhat mottled, there being depressed purplish areas alternating with more prominent light lobulations. The pleurae are shining but sprinkled posteriorly with small bright red petechiae. The bronchi are hyperaemic and some of them filled with yellow purulent exudate. The lymph nodes at the hilus, up to 1 cm. in size, are hyperaemic, succulent and without pigmentation. On section the upper lobe is air containing, except for the tongue shaped lower anterior portion, which is completely collapsed and presents a pale, smooth, airless surface on section. The lower lobe is much more hyperaemic. On section it shows extensive areas of consolidation, which are quite prominent above the aerated portion. They are granular and mottled grayish red and permit little exudate to be scraped off. These areas occupy large more or less wedge shaped areas at the extreme base of the lower lobe and show more or less distinct peribronchial distribution. In places the pneumonic process seems to have gone on to the formation of small abscesses filled with thick creamy pus.

The right lung superficially resembles the left. The anterior portions are extremely pale and emphysematous, the posterior dark purplish, with light areas somewhat depressed, below the level. On the posterior surface there is a fine fibrinous exudate. Numerous petechial hemorrhages are scattered over the pleura. On section areas of lobular consolidation resembling those on the other side are present in both upper and lower lobes, occupying the posterior half of the upper, and the greater portion of the lower lobe. There are also a few inconspicuous areas in the middle lobe. All of the bronchi are filled with a thick purulent exudate.

Heart.—Normal in size. Weight, 64 gm. The epicardial fat is scant in amount. The epicardium is smooth and glistening. The heart muscle, as seen from the outside, is pale and dotted here and there with small hemorrhagic spots 1 to 2 mm. in size and small grayish yellow areas of opacity which are apparently not related to the hemorrhages. The right auricle contains a pale chicken-fat clot. The foramen ovale admits a fine probe. The tricuspid valves and pulmonary cusps are normal. The right ventricle measures 2½ mm. in thickness. It is rather moist and swollen. The left auricle is normal. The mitral valves are the seat of fresh thrombotic papillary vegetations, which are situated near the margins of the valves and extend down along the margins of the chordae tendinae as far as the apices of the papillary muscles. These vegetations are gray and very friable and soft and but loosely attached to the underlying valves. On tearing them off, they leave a slightly roughened endocardium. The mitral valves themselves are rather thick and dilated, the parietal musculature is flattened. The ventricle measures about 5 cm. in length. The endocardium over the septum shows a somewhat streaky opacity, and shining through are seen irregular opaque yellow spots similar to those described on the surface. The muscle of the ventricle is about 9 mm. in thickness. It is pale and moist and on section shows sharply circumscribed dull yellow gray patches, one of which in the upper portion of the ventricle extends through the wall. The aortic valves are normal. The aorta measures 33 mm. over the sinuses.

Spleen.—Weight, 20 gms. Measurements, 7 x 4 x 2½ cm. Capsule smooth and tense. The surface is rather mottled with dark purplish and paler grayish red areas. Near the upper pole there is a pale gray sharply circumscribed area 3 by 8 mm., surrounded by a hyperaemic zone, obviously a small anemic infarct. On section the splenic pulp is rather pale, very firm and smooth and mottled with dark hemorrhages. The follicles are quite numerous but very small. The trabeculae are more in evidence than ordinarily.

Liver.—Weight, 365 gms. Measurements, 15 x 10 x 5 cm. The surface is smooth, the lower border sharply defined. Seen through the surface of the right lobe are more or less sharply circumscribed areas, in which the center of the lobule appears to be represented by opaque yellow spots less than 2 mm. in diameter, about which the liver tissue seems gray and translucent. The margins of these areas are somewhat hyperaemic. On section the same appearance is distinctly seen. The yellow portions lie around a very translucent gray tissue without other lobular markings. There are also minute punctate hemorrhagic spots in the parenchyma.

Adrenals.— Each weighs 3 gms. Normal.

Kidneys.—The capsule is easily peeled. The surface is smooth but profusely sprinkled with larger and smaller hemorrhagic areas. These range from barely visible punctae to larger blotches several mm. in size. There can also be distinguished against the yellowish background minute yellow points, and slightly more prominent circumscribed grayish yellow areas, the largest of which in the right kidney, is 1 to 2 mm. in diameter and surrounded by a hyperaemic zone. On section the renal tissue is extremely soft and moist and bulges above the surface of the capsule. The general color is pale grayish pink, but it is profusely blotched with smaller and lighter hemorrhages. Some of these are present also in the pyramids, although they are chiefly confined to the cortex. The glomeruli are extremely prominent. Many of them are surrounded by a zone of hemorrhage. This condition is confirmed by inspection with a hand lens. Pale areas on the surface extend a variable distance into the cortex as wedge-shaped necrotic pale grayish yellow areas with a yellow border. The pelves are free from hemorrhages. The mucosa is normal. The ureters are normal.

Bladder normal.

Uterus and appendages normal.

Tongue normal.

Pharyngeal lymphadenoid tissue seems rather hyperplastic and there are a few minute hemorrhages.

Tonsils normal.

Stomach.—Contains brown shreds mixed with mucous. The mucous membrane is pale and dotted with pink petechiae.

Intestine.—Contains a small amount of unformed fecal matter. The Peyer's patches are somewhat hyperaemic, but not prominent. The solitary follicles are inconspicuous both in the small and large gut. The mesenteric lymph nodes are quite numerous and of a bright red color. Section through some of the larger ones show grayish opaque areas of necrosis.

Pancreas normal.

Bones.—The epiphyseal lines are normal.

Brain.—The calvarium and dura mater are normal. The cortical vessels are engorged with blood. The brain tissue on section is hyperaemic. The cortex is purplish blue and the blood punctae numerous. The ventricles are normal.

Middle ears.—On both sides they show marked congestion of the mucous membranes, the cavities being filled with thick greenish pus.

The microscopical examination was as follows:

Myocardium.—The muscle fibers appear somewhat vacuolated. The striations are very indistinct. The nuclei are small and pycnotic. Definite areas of necrosis, however, and inflammatory changes are not evident in the section. One of the larger veins is plugged by a large hyaline thrombus.

Thyroid normal.

Pancreas normal.

Tonsils.—In one of the crypts the epithelium, which is elsewhere normal, shows ulcerations, the lymphoid tissue being covered by a necrotic exudate. Scattered through the otherwise normal lymphoid tissue there are a few inflammatory foci surrounded by fibroblasts and containing nuclear detritus and bacteria.

Lymph nodes.—Many of the lymphoid cells are pycnotic; some of the vessels containing hyaline thrombi. Some of the nuclear fragments are taken up by phagocytes. There are acute degenerative changes.

Liver.—The central portions of the lobules are composed of liver cells showing varying degrees of fatty infiltration. The nuclei are well stained and there is no evidence of necrosis.

Hypophysis.—Hyperaemic. The oxyphilic cells predominate. The pars nervosa is normal.

Adrenal.—Normal.

Brain.—Section through the cortex shows normal nerve cells.

Kidney.—The section shows an anemic infarct, evidently recent since the glomerular and vascular structure is still present in places. There is marked leucocytic invasion between the necrotic tubules. At the margin of the infarct the vessels are distended with blood. In the intact portion of the kidney the convoluted tubules are dilated with low flattened epithelium. Many of the Henle tubules contain hyaline or waxy casts. The interstitial tissue is oedematous but not increased in amount. The glomeruli are apparently normal.

Lungs.—The alveoli throughout, save for a small area, are filled with an exudate composed almost wholly of polymorphonucleated leucocytes in a rather dense fibrinous plug. There has been destruction of the alveolar septa with the formation of small abscesses. The bronchi are filled with a purulent exudate, the epithelium being well preserved. In places there is a little fresh fibrinous deposit on the pleura.

No bacteriological report was made.

Infectious endocarditis in young children is very rare. Heubner reports a case of infectious endocarditis in an infant of ten months old. He speaks of the rare association of an infectious endocarditis with the virulent form of measles in which the blood culture often shows the presence of streptococci.

This case is presented not because it differs in any respect from the majority of cases of infectious endocarditis, but because of its occurrence at so early a period of life, and it is also of interest because of occurring in the course of measles.

PRESENTATION OF SPECIMENS.

D. FELBERBAUM, M.D.

Papillary Adenoma of Kidney.—The first case is a specimen removed from an individual who was about sixty years of age and who had a very extensive and extreme form of chronic articular gout. Besides this, he had an immense abdominal tumor, filling up the entire left half of the abdominal cavity. While he was an inmate of the Montefiore home, he had numerous attacks of severe hematuria. He died rather suddenly this year. At autopsy, this large tumor was found, weighing almost fourteen pounds, with extensive metastatic nodules throughout both lungs and one large tumor mass in the right lobe of the liver. At first, from the gross specimen it was thought to be a hypernephroma; it was very yellowish and quite broken down. On subsequent examination, it proved to be a papillary adenoma of the kidney. Sections from the primary tumor and from the metastases showed the same structure.

Unusual Form of Liver Tuberculosis.—The next specimen is a rather unusual form of tuberculosis in the liver, in which the tuberculous deposits take on a large nodular form. This man was 52 years old, and was admitted to the Montefiore Home on May 8, 1907. His history dated back eleven months prior to admission, when he first complained of severe abdominal pain. He had never had blood in the stools, diarrhoea or jaundice, but was considerably emaciated, and presented large lymph-nodes. The liver felt smooth and hard on palpation. In August, 1907, the nodes in the left groin suppurated, the discharge continuing for a year when it ceased spontaneously. He began to gain weight until the early part of December, 1910, when he developed a cough, hectic temperature, and again rapidly emaciated. Numerous blood counts showed degeneration of the red cells. A gastric analysis was negative.

At autopsy, there were found many old tuberculous retroperitoneal lymph-nodes. The stomach was normal. The liver was studded throughout with irregular masses, varying in size. These were sharply outlined from the liver tissue, and showed a depression on the surface. There were a few areas of hemorrhage in the liver substance. The kidneys showed parenchymatous degeneration.

On microscopic examination, the nodular masses, which were at first thought to be cancers, were found to be formed by conglomerate tubercles, surrounded by areas of round cell infiltration and many giant cells. Tubercle bacilli could be demonstrated.

Spontaneous Rupture of the Heart.—The next specimen is a case of spontaneous rupture of the heart. The subject died May 7, 1906. He was an inmate of the Montefiore Home for ten years, with cerebro-spinal spastic paralysis. Death occurred suddenly. The pericardial sac was found to be distended with recent blood clot and about 500 cc. of fluid blood. The left ventricle showed along the line of the coronary artery, a tear one and one-half inches in length. The edges of the tear were ragged and the adjacent tissue rather spongy. Dr. Harlow Brooks found on making sections that the tissue about the tear showed gummatous infiltration and a great deal of degenerated material through which the rupture had taken place.

Discussion.

Dr. Ewing: I was partly responsible for the mistaken diagnosis in the first case. This was quite a remarkable tumor and as we are accustomed to remarkable conditions at the Montefiore Home, I thought it was quite in line that we should have a curious hypernephroma.

However, it proved to be quite different in that it perfectly preserved the shape of the kidney, whereas hypernephromas, after reaching a certain dimension, are apt to be rather irregular in shape. On gross section of this enormous tumor the separation of renal substance from the tumor was not so sharp as is usual in hypernephroma. On the other hand, the general appearance of the gross section strongly recalled what one is accustomed to see in hypernephroma. The large blood content, cysts filled with blood, highly pigmented yellowish areas, and the general conformation, strongly recalled hypernephroma.

On microscopical section we find something entirely different. In view of the present discussion as to the origin of hypernephroma, it seems to me that we have here a standard on which we may proceed with the discussion of the renal origin of various tumors differently interpreted by different authors. For here is a renal tumor with structure having no resemblance whatever to the ordinary hypernephroma, and evidently derived from the kidney tissue.

NERVE FIBRILS IN THE SINO-AURICULAR NODE.*

B. S. OPPENHEIMER AND ADELE OPPENHEIMER.

Although several observers (Wilson,[1] DeWitt,[2] Engel[3]) have succeeded in staining the nervous elements (fibers, fibrils and ganglion cells) in the *auriculo-ventricular* system of the heart, no one has thus far described all these structures in the *sino-auricular* node. Wilson was the first to demonstrate by means of a vital stain, not only the nerve-fibers accompanying the bundle of His, but also ganglion cells of various types and a rich plexus of nerve-fibrils intimately related to the specialized musculature of the conducting system. The bundle of His may therefore be considered anatomically a neuro-muscular structure. As the region of the sino-auricular node of Keith and Flack is now believed to be the pacemaker of the mammalian heart, we have thought it of importance to make a similar investigation of its nervous elements.

Subepicardial nervous elements overlying the sino-auricular node may be readily demonstrated with the ordinary van Gieson stain. As is known, there occurs here *over* the node a rich collection of ganglia and nerve fibers; and in the literature there is even an occasional mention of a nerve fiber or ganglion cell *within* the limits of the node (W. Koch[4], Schwartz[5]). But no one thus far has used a specialized nerve stain for the Keith-Flack node and consequently there has been no description whatever of nerve-*fibrils*.

We employed a vital stain of methylene blue, following for the Keith-Flack node the same technique as Wilson applied to the bundle of His. We report at this time only the results of using this method on the hearts of freshly killed pigs, bullocks and sheep, although the hearts of several other animals are being investigated.

In the pig, sheep and bullock, we found a plexus of nerve-fibrils in the sino-auricular node such as Wilson described for the auriculo-ventricular system. Fine fibrils with varicosities were seen intimately interwoven with the specialized musculature of the Keith-Flack node, and were also seen surrounding the special nutrient artery of the node. Such fibrils were identical in appearance with those which composed the nerve-fibers. In certain sections nerve branches from the subepicardial nervous structures seemed to penetrate the node.

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*Presented at the January meeting; manuscript received too late for publication in Vol. XII, Nos. 1 and 2.

In the pig's heart, there occurred in addition to these nerve-fibrils a multipolar ganglionic cell.

Aside from the subepicardial nervous elements, the sino-auricular node, therefore, contains *within* its limits, nerve-fibers and nerve-fibrils.

Sections showing nerve-fibrils in the sino-auricular node of the pig and bullock were demonstrated under the microscope, and a drawing presented.

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METASTATIC HYPERNEPHROMA OF THE LUNGS.

B. S. OPPENHEIMER, M.D.

By way of comparison with Dr. Felberbaum's case of papillary adenoma of the kidney with lung metastases, I should like to present a case of metastatic hypernephroma in the lung.

The patient from whom this specimen was obtained was a woman who was 57 years old at the time of her admission to Montefiore Home in June, 1910. She died March 15th, 1912.

The history in brief was as follows:

In 1906 she had an abdominal operation performed in

London, at which the left kidney must have been removed. In spite of several attempts it has been impossible to learn the nature of the kidney lesion at the time of this operation.

In 1908 she had a sudden attack of unconsciousness followed by paralysis of the left half of her body. After a stay at two of the New York hospitals, she was admitted to the Home as a case of hemiplegia.

At the time of her admission, physical examination did not reveal anything abnormal in her lungs. The radial arteries were markedly thickened. She had a left-sided hemiplegia with hemianopsia.

Toward the end of the year 1910, she began getting pulmonary signs and symptoms. Dr. Harlow Brooks was the first to suspect metastatic tumor of the lung. An X-ray of the chest taken at his suggestion was a decided help in revealing the presence of a growth in the left chest.

On March 17th, 1911, patient coughed up bloody sputum.

By October, 1911, the physical examination of the chest revealed an area of dulness on the left side with diminished voice and fremitus from the fourth rib down.

December, 1911, a marked distention of the veins of the axilla and chest was noted on both sides, more marked on the right than on the left. The thoracic wall showed several hard, thickened, tortuous arteries.

The patient became gradually more cachectic.

In February of the year 1912, exploratory aspiration of the right pleural cavity withdrew one ounce of bloody fluid which did not show tumor cells.

March 9th, 1912, patient was extremely emaciated and was coughing up large quantities of thick, purulent sputum without blood. The heart was apparently displaced to the left, with the apex beat at the anterior axillary line. There was a moderate oedema of the upper portion of the thighs, of the feet, and of the ankles. There were no bone metastases.

Patient died March 15th, 1912; that is about six years after the nephrectomy.

At autopsy the right lung was found to be very adherent and studded with numerous white nodules, varying in size from that of a pea to that of an olive. At the root was one as large as a small orange which had become degenerated and filled with a grumous material.

The left lung, the one here presented, shows one large interlobar tumor about the size of a hen's egg. This tumor was undoubtedly the one revealed by X-ray. It has a necrotic centre. In addition there are numerous smaller nodules, chiefly pleural or sub-pleural. These are firm, white, usually flattened, well circumscribed. The borders of the lung, especially the inferior border, have short fringes of tumor tissue.

The only remaining, that is the right kidney, showed a solitary cortical nodule which on microscopic examination presented the same histological structure as the tumors in the lung.

Microscopic examination showed that the tumor evidently belongs to the hypernephroma group although morphologically it is not a typical hypernephroma. Its peculiarity consists in the presence of numerous giant cells. With Sudan III fat could be demonstrated in the endothelial and tumor cells, and with the polarizing microscope Dr. Hanes proved the presence of anisotropic fat globules. The histological picture of hypernephroma is very variable as has been pointed out by Hall who studied a series of seventeen cases.

The question of the origin of renal hypernephromata from heterotopic adrenal tissue in the kidney is still under discussion. In a recent paper Glynn agrees with Stoerk, Zehbe, and Wilson and Willis, who contend that renal hypernephromata seldom if ever arises from adrenal rests. They believe, in one way or another, in the nephrogenic origin of the renal hypernephromata.

Discussion.

DR. EWING: I had an opportunity to look at the sections of the metastatic hypernephroma of the lungs, and I think it is worth noting that they present an unusual picture for hypernephroma. All or most of the pulmonary nodules present many large giant cells and if one has not seen this particular picture, it will enlarge his knowledge as to the remarkable forms these tumors may take.

EARLY OVUM IN A FALLOPIAN TUBE.

I. RUBIN, M.D.

An exceedingly early ectopic ovum.—This specimen, of which I shall show sections on the screen, was removed from a patient at Beth Israel Hospital in September, 1911. The patient was admitted to Dr. Bandler's service with symptoms of pain in the right side of the abdomen and hemorrhage. She was 23 years old, had been married two months, and began to show symptoms two weeks after her last regular menses, i. e.: five days before admission. Two days later, in addition to the cramp-like pains in the abdomen, she also noticed hemorrhage. On examination we found the uterus slightly enlarged and to the right side was a fairly movable mass of firm consistence. There was no blood at the time of this examination. The tentative diagnosis of ectopic gestation was made; a preliminary curettage was then done for diagnostic purposes. The curettings, however, did not point to intra-uterine pregnancy, but, in view of the clinical history, Dr. Bandler deemed it advisable to open the abdomen. There was no blood, either free or clotted, anywhere in the peritoneal cavity. On the right side, however, the ovary was seen to be twice as large as compared with the left ovary, and contained a large hemorrhagic mass. The latter resembled a hemorrhagic corpus luteum. At the same time ovarian pregnancy had to be thought of. The right ovary and the greater portion of the right tube were removed en masse. A small portion—about ¾ of an inch in length—of the isthmical tube was left in situ. A hasty examination of the excised portion of the tube showed that a few drops of blood could be expressed from the fimbriated end. In view of this finding, and also to complete the anatomical study to prove an ovarian pregnancy, should this latter be the case, I thought it advisable to resect the residual portion of the tube, to which Dr. Bandler readily consented. I was surprised to find, on rolling this isthmical portion of the tube between my fingers, a small nodule of the size of a very small pea. The sensation was so curious and so suggestive that I asked several gentlemen to palpate it. I fear the specimen must have suffered as a result of this manipulation.

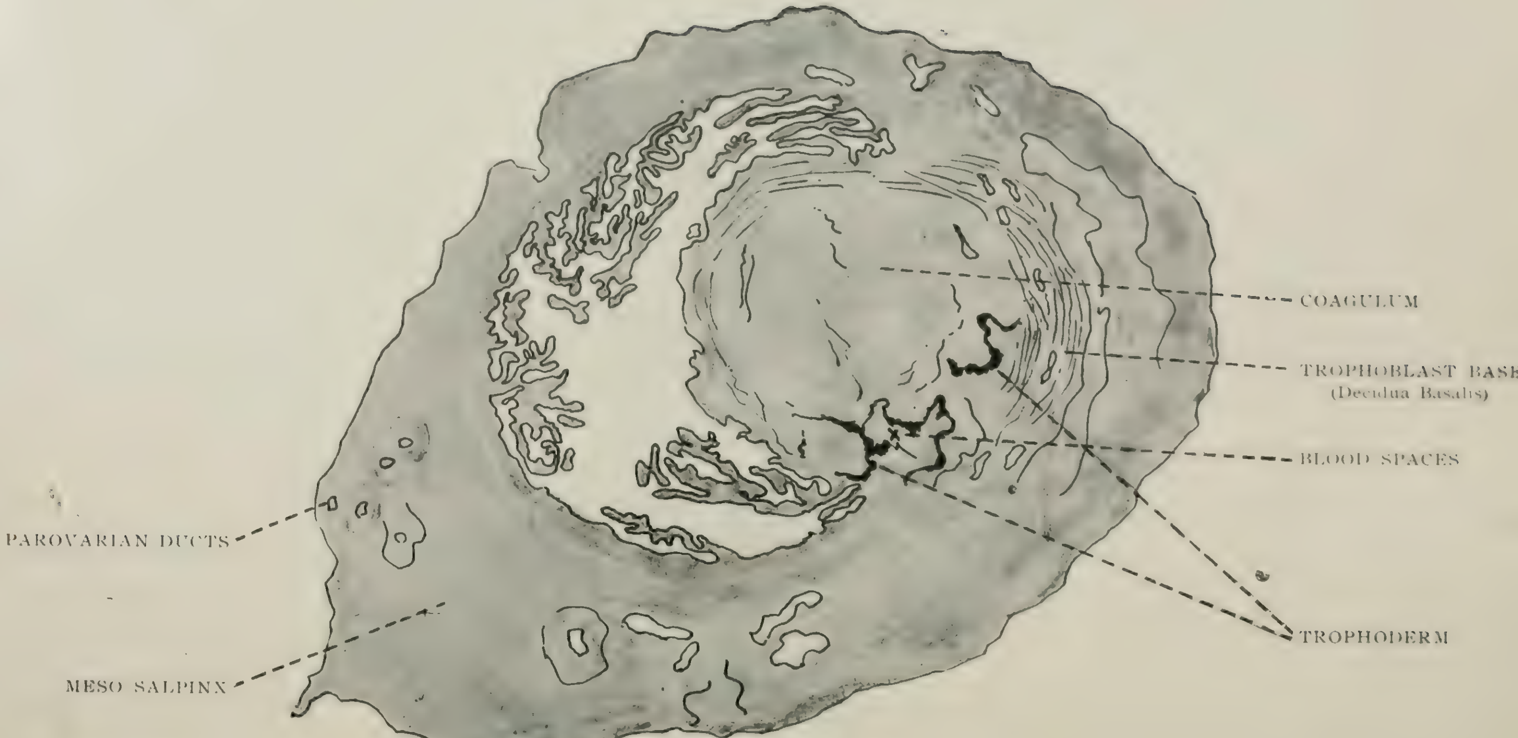

Fig. I. Distal Half (x 15 Diameters) — Cross-Section

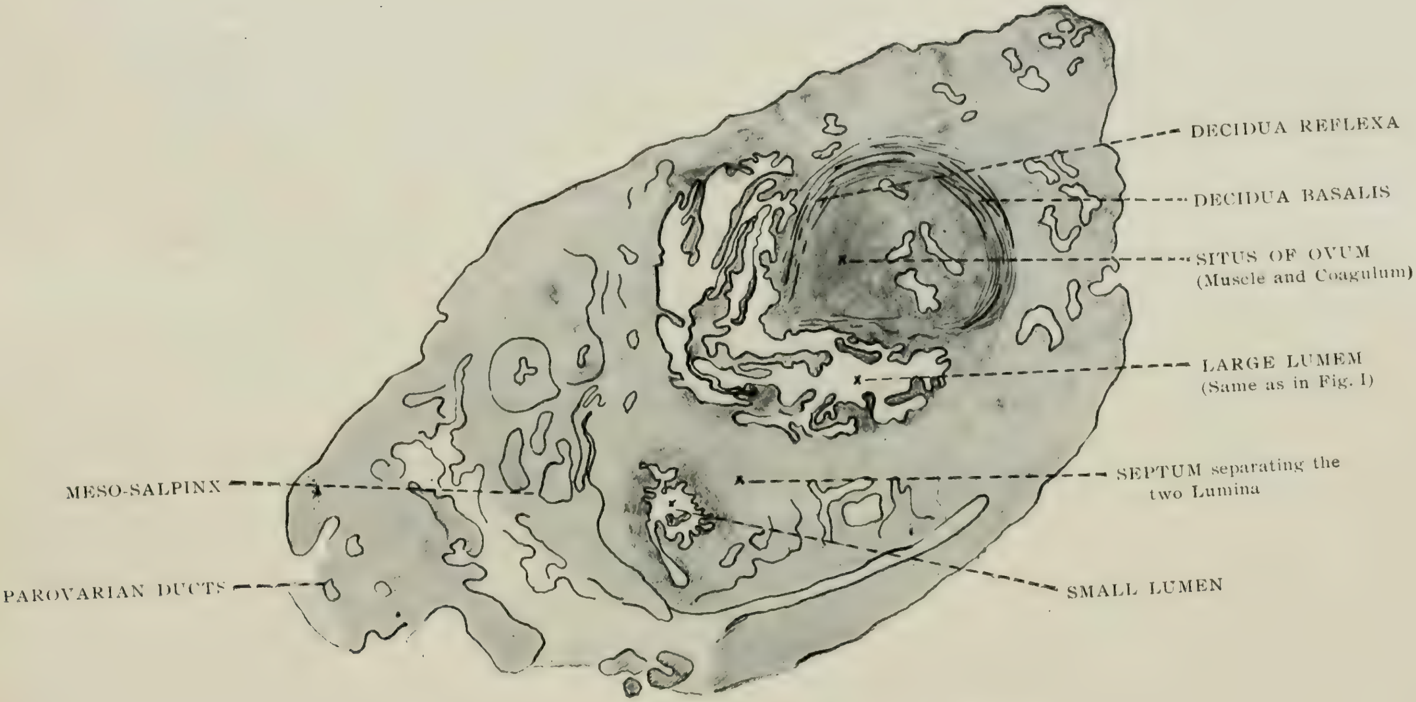

FIG. II. PROXIMAL HALF (x 15 DIAMETERS) — CROSS-SECTION

Camera Drawing

Demonstration of the Sections.

The nodular portion of the tube was divided at about its middle point after hardening. It showed a rather firm coagulum attached to one wall, resembling the picture of an ectopic mass on section. Either half of this nodule was then blocked and cut serially. Unfortunately a number of sections were thus lost; the series, however, shows a very clear picture of an exceedingly young ovum in the tube. The distal half shows a coagulum attached to the superior wall of the Fallopian tube and occupying about one half the width of the tube. Only one third of its circumference is attached. It measures at its greatest diameters 3x3.5x3.75 millimetres. The tube is apparently not enlarged and would correspond to an average tube at this point, i. e., 5x6 millimetres. At the base of the coagulum are seen two masses of trophoderm, from which are given off several streaks of trophoblast, which stretch toward the outer and the inner portion of the ovum and enclose between them fresh blood cells. The ovum itself is intimately connected with the muscularis, its base rests upon several layers of large pale and more intensely stained fusiform and large polymorphous cells, which form the decidua basalis. The circumference of the coagulum is lined by one or two layers of the same sort of cells, which may be taken to represent the decidua reflexa. These cells, however, are in a very poor state of preservation. Here and there throughout the coagulum may be seen small clusters of trophoblast cells. The embryo as such can, however, not be made out. The tubal epithelium fringes the margin of the ovum a little above its point of insertion on either side. The few adjoining tufts show a varying number of decidua cells. The musculature also shows a small number of these wandering decidua cells close to the base of the ovum. There is a small amount of leucocytic infiltration immediately underlying the base of the ovum, *but this is conspicuously absent in all the other elements of the tube.* The ovum gets smaller and smaller as we approach the fimbriated end, and is finally seen to consist of a small blood clot in connection with one column of the tubal epithelium and then to disappear altogether. The tube itself beyond this point shows nothing abnormal.

Followed toward the uterine end of the tube, the trophoderm quickly disappears; instead there is only the trophoblast capsule with well marked decidua basalis. At this point there is pronounced hypertrophy of the muscle. A great number of muscle fibres are seen to penetrate the coagulum. The margin of the latter is almost completely enclosed by a single layer of tubal epithelium. The entire coagulum is much smaller than that of the other half, as above described, and fills only a small portion of the tube lumen. But here we also encounter another smaller lumen in the vicinity of the broad ligament. This lumen is lined by columnar epithelium, which is thrown into very primitive tufts, and resembles in general the histologic picture of the isthmical portion of the tube. A broad muscular septum separates these two lumena. As we follow this series toward the uterine end, these two lumina show a variation in size, so that soon they are of equal width when there begin to appear small channels at the same side of the insertion of the ovum lined by tubal epithelium, which connect the two. Presently the septum gets thinner and smaller, the two lumina communicate broadly, the ovum almost disappears, while its muscular bed is very conspicuous. The septum itself disappears entirely and is only represented by a local thickening of the muscularis. The tube beyond this point shows nothing exceptional.

This brings us, I think, to the question of etiology of ectopic gestation. Explanations so far are numerous, and by no means altogether established. The difficulty in the study of the etiology of ectopic gestation lies in the fact that material dealing with the very early stages has been exceedingly scarce. We have even come upon our case quite by accident, although clinically the presumptive diagnosis of ectopic gestation was justified. Ectopic gestations as ordinarily studied for purposes of pathogenesis already show a certain amount of intra-capsular or extra-capsular hemorrhage, and a certain amount of inflamation. The inflamation may be secondary to the ectopic as well as a primary cause et the same. It is desirable, therefore, to have an ovum which had not proceeded to this stage. Our specimen shows a complete absence of inflammatory changes. Instead we find a muscular spur at a portion of the tube where the lumen is ordinarily narrow. It would seem that the ovum, in traveling toward the uterine end of the tube, had encountered this spur, which acted in a purely mechanical way, and then penetrated the mucosa and embedded itself into the hypertrophied portion of the muscularis. Whether this was intra-columnar or columnar is rather hard to say. The muscular spur, in conjunction with the local muscular hypertrophy would serve as a direct obstructing cause. The small diverticulum which dips down toward the mesosalpinx is situated toward the proximal side of the septum, and hence cannot be considered as a factor in the etiology of this ectopic gestation. The condition is rather one which resembles the intermuscular division of the tubal epithelium, as first described by Werth and Futh, and also the partial attempt at a duplication of the tube, as described by Goebel. I think that in this case we might reasonably say that the cause of the lodgment of the ovum in the tube is purely a mechanical one, and was due to an anomalous overgrowth of the musculature, plus a muscular septum formation, which together narrowed the normally small lumen at the isthmical portion of the tube and rendered impossible the progress of the ovum toward its normal goal—the uterus.

Discussion.

DR. STEWART: Might it not be possible that there is another explanation for the thickening of the muscle coat around the ovum. Is it not true that when the ovum grows in the tube there is a hypertrophy of the tubal musculature, just exactly as you get in the uterus? This muscular enlargment might therefore be more the result of the tubal implanation, than its cause.

DR. EWING: I would like to ask if any villi were found in gestation.

DR. RUBIN: I think that it is rather likely that the hypertrophy of the musculature may have followed the lodgment of the ovum, except that this would not account for the septum formation at the same time. Nor would such hypertrophy be so peculiarly eccentric.

There were no chorionic villi found. The ovum itself is exceedingly young, I think. As far as I have been able to see, it is probably the youngest ovum in a tube that has been demonstrated. That shown by Futh in 1899 was supposed to be two weeks old but it was very much larger than the one shown in my specimen, and in the light of most recent investigations, notably those of Teacher and Bryce, must have been much older than was originally estimated. My specimen, though much larger than Leopold's ovum in utero shows almost identical pictures. Though it is not possible to determine its exact age, it is safe to assume that it is younger than 14 or 15 days.

THE EFFECTS OF COLD ON ANIMAL TISSUES.

ROBERT A. LAMBERT, M.D.

(From the Department of Pathology of the College of Physicians and Surgeons, Columbia University.)

The effect of cold on the animal organism, though full of interest and perhaps of greater practical importance than the effect on individual tissues, will be left for discussion at some future time. While closely related, the two questions should not be confused. Principles governing the effect of cold on the body do not necessarily apply to the effect on its constituent tissues. It is an interesting, and well recognized fact, that isolated mammalian tissues, or even entire organs, can withstand temperatures far below that fatal to the body as a whole.

In considering the effect of low temperature on animal tissues, the first question which arises is: Is the injury due to the low temperature itself or to the associated freezing? This question had been definitely settled in regard to many plant cells and protozoa through the process of "over-cooling," a well understood physical phenomenon in which the temperature is lowered just under the freezing point without allowing freezing to take place. Such experiments with a number of plant cells have shown that the injury is, for the most part at least, to be attributed to the freezing. We have applied practically the same principle to studies with animal cells—tissues of the chick embryo—with the following technique: Hanging-drop culture preparations, composed of small bits of tissue in coagulated plasma, were placed for forty-eight to seventy-two hours in an ice box at —7° to —8° C. a temperature around the freezing point of chick tissue. When removed from the ice box some of the preparations were found to be frozen, while others were not, a result to be attributed no doubt to accidental variations in the salt content of the drops of plasma due to evaporation. The number of frozen or unfrozen preparations can be more definitely controlled by purposeful variations in the salt content of the plasma, a procedure which experience has shown is not of itself in any way harmful. Such frozen cultures do not show upon subsequent incubation any growth phenomena whatsoever, while the unfrozen cultures grow practically as well as the controls which have not been exposed to cold at all. This experiment demonstrates then a striking contrast in the effects on animal tissue produced by freezing and by subjection to a temperature around the freezing point at which the tissue remains unfrozen. The experiment, however, does not settle the question as to whether *prolonged* exposure to a temperature just above the freezing point may not be in some degree harmful.

The results of another series of studies throws some light on this point. A comparison was made of the duration of life of embryonic chick tissue kept in hanging drop cultures at room temperature (+15 to 18° C.) and at a temperature a little above the freezing point (—4° to —6° C.). At the end of different periods (two, three, four, five, six, seven, eight, ten and fifteen days) the pieces of tissue were transferred to fresh drops of plasma and placed in the incubator at 37°. Two-, three-, four- and five-day preparations in both series gave good growths. Preparations kept for longer periods in the ice box showed proportionately lessened growth, and after ten days exposure were always negative. On the other hand, those kept at room temperature for ten days were uniformly positive, and growths were occasionally obtained from fifteen-day preparations.

These experiments show then that embryonic tissue may be kept alive longer at room temperature than at a temperature just above the freezing point of the tissue. This lessened vitality at the lower temperature may perhaps be interpreted as the result of some derangement in the metabolism in the cell leading to an accumulation of injurious products. An instance of disturbed metabolism due to the effects of cold, one that has received careful study, is seen in the sweetening of potatoes in winter. The cold does not inhibit the activity of the diastase normally present, whereas oxidative processes are greatly retarded, with the result that sugar accumulates (Müller-Thurgau).

It has been observed clinically that limbs exposed to cold for any considerable period, though not frozen, may yet suffer the serious injury known as "frost gangrene." The question as to whether this is a result of a direct cell injury or of an indirect injury through circulatory disturbances, was a subject of much discussion among early workers. Later investigations have shown, however, that this gangrene is due to ischaemia. It was urged by Cohnheim and others that the ill effects of freezing upon the body tissues are likewise primarily due to circulatory disturbances in the part frozen, but it is now agreed that the process of freezing injures the cell directly.

The injurious action of cold on animal tissues is then of two kinds, one direct and toxic in character, the other nutritional.

In the process of freezing how is the injury to the cell brought about? The mechanism of cell freezing will be made clearer by a consideration of the freezing of a salt solution, and of some colloid such as gelatin. Ice forms in salt solution from the water present leaving the salt in concentrated form between the crystals. Gelatin, upon freezing, is left in firm layers between the particles of ice. The process of freezing of plant cells and protozoa has been directly observed under the microscope. Ice crystals are formed as in salt solutions and in gelatin from the water present. If the cells are quite large (amoebae, phycomyces) the crystals form inside as well as outside the cells. In small cells the crystallization is always extra-cellular. In either case there occurs a marked distortion of the cell body.

The injurious effects of freezing upon cells may be explained in several ways: (1) Through mechanical tearing as the ice crystals are formed. (2) Through the concentration of salt around the crystals. (3) Through the withdrawal of water in the process of ice formation. In regard to plant cells the evidence is strong in support of the view that the withdrawal of water is the chief factor. The experiments supporting this explanation can not be detailed at this time. A certain parallelism has been found to exist between the phenomena of resistance to freezing and to drying by lower forms of life. It has been maintained that in both instances the essential factor is the withdrawal of water from the cell.

Does the injury to the cell or tissue from freezing take place in the freezing or in the thawing? And does the rapidity of thawing influence the degree of injury? Both of these questions have interested botanists. The first presented a difficulty in the matter of separating the effects of freezing from those of thawing. Goeppert, however, using two flowering plants, orchid and begonia, which in death undergo a change in color, was able to show that death took place while the cells were in the frozen state. Similar studies by Molisch with several fluorescent algae added further support to Goeppert's conclusion that the injury produced by freezing is associated with the process of crystallization. Goeppert maintained that it necessarily followed from his work that the rapidity of the thawing was a matter of indifference, but other investigators felt that on account of the limited application of such tests the question as to the possible influence of rapid or slow thawing could not be considered superfluous. In order to settle this point Molisch and Müller-Thurgau, working independently, carried out experiments in which several hundred plants and certain fruits were used, comparing the results after slow and after rapid thawing. They found that with only three exceptions, all fruits (apple, pear and guava) the rate of thawing did not modify in any way the effect produced by freezing.

What is the effect of subjecting tissues to temperatures below the freezing point? It would seem at first from the preceding analysis of the injurious action of freezing that after a tissue is completely frozen a still lower temperature could produce no further injury. But this has not been found to be the case. It has been shown furthermore that the *duration* of exposure to cold is an important factor. The results of our experiments bearing on these two points—depth of temperature and duration of exposure—are as follows: Pieces of chick embryo heart survive freezing at —10° C from two to six hours but are killed by exposure for twelve or more hours. The same tissue resists a temperature of —20° for five minutes but not for twenty minutes. Lower temperature obtained with a carbon dioxide freezing apparently produces a fatal injury in less than a minute. Rischpler's studies upon the effects of freezing animal tissues in situ (rabbits' ears) support the general law, exemplified in the above experiments, that the effect of low temperatures is directly proportional to the depth of the temperature and to the duration of exposure.

The question as to why this should be so has not been satisfactorily answered although several hypothyses have been offered: (1) That certain elements of the cell (e. g. lipoids) are frozen at lower temperatures than the water present. (2) That the crystallization of water, and the consequent drying of the cell, becomes more complete with a longer exposure and a lower temperature. (3) That serious chemical disturbances are produced by very low degrees of cold. (4) That low temperatures affect differently the various metabolic processes in cells, thus causing an accumulation of toxic products. None of these hypothyses is altogether adequate.

The varying resistance to cold of different mamalian tissues has received considerable attention. The ears of guinea pigs and rabbits and the tails of rats and mice are well adapted to such studies. The abdominal viscera, while offering some difficulties for carrying out experiments of this nature, have likewise been subjected to experimental study. Ice-salt mixtures and ether spray have been chiefly employed to induce cold. Morphological studies have shown that if the part be completely frozen all tissues (epithelium, connective tissue, muscle, bone, cartilage, etc.) give evidence of being at least temporarily injured. Shrunken nuclei and vacuoles in the cytoplasm are regularly seen. Prolonged freezing or subjection to very low temperatures causes necrosis. Short freezing repeated at intervals produces, especially in epidermis, a remarkable hyperplastic growth. Atypical division figures and large multinucleated giant cells are found in large numbers in tissue so treated. Certain tissues are much more susceptible to cold than others. The secreting cells of the liver and kidney are easily killed; bone is less resistant than cartilage; muscle is more susceptible than connective tissue. It may be stated summarily that to cold as to other injurious agencies, the more highly specialized cells are least resistant. An apparent exception to this rule appears in the work of Richardson (1867) who stated in his report that the freezing of a pigeon's brain produced only temporary irritative phenomena, and that a pigeon whose cerebral cortex had been frozen forty-five times remained perfectly normal. The fact that he employed an ether spray on the skull in his attempts to produce a frozen condition renders it highly improbable that the brain was frozen at all.

In our tissue cultivation studies the only thorough comparative observations made were with heart muscle and connective tissue of the chick embryo. The latter proved the more resistant but the difference was not as striking as might have been expected. Pieces of heart would occasionally resume beating, upon incubation, after having been frozen three or four hours at

—10°, while six to twelve hours represented, as a rule, the limit for connective tissue.

The great resistance of cancer cells to freezing and low temperatures is well known. Ehrlich found, for example, that a mouse carcinoma frozen for two years at —10° to —14° was still transplantable. Gaylord made comparative studies of the resistance to an extremely low temperature of cancer cells and embryonic cells, inoculating the tissue after exposure as a test of survival. He found that mouse carcinoma cells survived the temperature of liquid air (—180°) for eighty minutes, while the tissues of the mouse embryo were killed by twenty minutes exposure.

We have made similar comparative studies. Instead of transplanting the treated tissue, however, the method of tissue cultivation has been used as a test of survival. The results have confirmed the work of Gaylord as to the greater resistance of malignant tumor cells as compared with embryonic cells. We have also made comparisons between sarcoma cells and connective tissue cells of adult rats. Cultures from both embryonic and adult tissues frozen five minutes at —16° were regularly negative while tumor tissue treated in the same way gave uniformly positive cultures, although growth was less active than with untreated tissue. That embryonic tissue of the chick is much more resistant to cold than mouse embryo tissue is also shown by these experiments.

The last point to be discussed is the effect of interrupted freezing, that is of repeated freezing and thawing, as compared with that of continuous freezing. It has been currently accepted that a fatal cell injury may be produced more rapidly and with greater certainty by interrupted freezing than by continuous freezing. Theoretically there is some basis for this belief inasmuch as the factor of mechanical tearing would apparently be increased. It has been shown too that red blood corpuscles of several species are not readily destroyed by freezing once but are easily broken up by repeated freezings. Rigid experimental proof of this principle as regards other animal tissue cells, is, however, difficult to find.* On the contrary, considerable work has been done which indicates that the duration of exposure and the depth of the temperature are much more important factors. Fuerst, for example, found that freezing a rabbit's ear eight times with intervals of fifteen or thirty minutes between the freezings does not cause any marked destruction of tissue, whereas it has been shown by Rischpler and others that ten to thirty minutes continuous freezing is followed by wide-spread necrosis and sloughing.

Summary.

1. Low temperatures associated with freezing produce a direct cell injury. The injury is probably produced through the withdrawal of water in the process of crystallization.

2. Temperatures slightly above the freezing point, are harmful if long continued. In extremities the result is gangrene from circulatory disturbances. With cultures of chick tissue the effect is probably due to a derangement of cell metabolism.

3. The influence of the rate of thawing is negligible.

4. The effect of extremely low temperatures is proportional to the duration of exposure and depth of temperature.

5. Body cells vary in their resistance to cold. The highly specialized organ cells show least resistance. Cancer cells are more resistant than the cells of normal adult and embryonic tissues.

6. Repeated freezing of an extremity produces less harm than a single long continued freezing. Short freezing at intervals induces in certain tissues a remarkable hyperplastic growth. Long continued freezing is followed by complete necrosis and sloughing.

*Recent experiments with pieces of chick embryo intestine have shown that while a few cells grow out in cultures after rapid freezing and thawing three times, a more diffuse growth takes place from tissue frozen continuously at the same temperature (-16°C) for the same length of time; that is, a somewhat greater injury is produced by interrupted freezing.

Discussion.

Dr. Stewart: It is very surprising how many contradictory reports one finds in the literature regarding freezing. I have read numerous papers that have been written regarding the effect on life of freezing. One man will say emphatically that the frog can be frozen stiff and another will say just as positively that it cannot.

Referring to the difference between the resistance of cancer cells and embryonic cells this seems very important, because it was the tendency before Dr. Lambert's paper to regard the destructive effect of freezing as a purely mechanical process. His work, however, shows that the mechanical theory does not explain all. Here is a cancer cell which is frozen just as hard and an embryonic cell, and yet the one lives and the other does not. There certainly must be a more deep seated process than the mechanical process.

Dr. Lambert: The cells of the transplantable rat and mouse tumors show a far greater resistance to cold than either the normal or embryonic tissues of these species. Embryonic chick tissues, as I stated before, are more resistant than those of rats and mice.

I emphasized the point as to the difference in the effects produced by interrupted and by continuous freezing because it is a current belief that the former produces the greater injury, an opinion so far as I have been able to ascertain, not based on experimental work.

The reader whose interest leads him further into this subject will find in the two following treatises references to the literature:

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DR. W. G. MACCALLUM, *President.*

HYPOPLASIA OF THE KIDNEYS.

F. R. MOUNT, M.D.

The organs here presented were taken from a foundling baby, admitted to the New York Nursery and Child's Hospital, March 26, 1912, aged 14 days, on the service of Dr. Kerley, to whom I are indebted for the report of the clinical history. It was in poor physical condition on admission, and during its stay of ten days gradually lost, dying apparently of inanition; weight shortly before death was 4 lbs. 5 ozs. There was no record of urination, but it is improbable that dry diapers would have passed without notice.

Autopsy was performed April 5th, 24 hours post mortem. Male child, white, poorly nourished, 46 cm. in length. Feet in attitude of moderate equinovarus, more marked on the right side; no other deformities apparent. Aside from the urogenital organs, there were no important changes in the viscera. The kidneys did not present the usual retroperitoneal prominences alongside the vertebral column, but their positions could be identified by the distinct course of the ureters. Adrenals, kidneys, ureters, and bladder were removed together. The adrenals appear of normal size, color, and consistence; section shows the usual midzone hyperemia.

The right kidney is slightly smaller than the left, each being smaller than its corresponding adrenal; the contrast is exaggerated, due to the depth of the concavities on the under surfaces of the adrenals which the kidneys occupy. The surface of the right kidney except for indistinct lobulation is smooth; on section the cortex is 1 mm. thick, the medulla 3-4 mm. The hilus is completely filled with dense tissue occupying the usual position of the pelvis. The lumen of the ureter appears to end blindly in a slight enlargement; the apices of the papillæ are thus separated from the ureteral cavity by a wall of tissue varying from 1 to 3 mm. in thickness. The surface of the left kidney has scattered nodular prominences, slightly paler than the surrounding kidney tissue, from 1 to 3 mm. in diameter. Some are solid, others distinct thin-walled cysts. On section the cortex is about 1 mm. thick: pyramids are of very unequal size and shape, the outlines being partly obscured by the presence of fairly well-defined yellowish white nodules. Vessels are injected, but the markings are extremely irregular. There is a large amount of tissue in the region of the hilus, as in the right kidney. The ureters were not probed before fixation. In the lower portion they appear of normal caliber but the wall seems thick and nodular. Nearer the kidneys the lumen is distinctly narrowed. The bladder is contracted, and contains a small amount of clear urine; there was, therefore, some secretion by the kidneys. In tracing the vas deferens, no seminal vesicle could be found on either side.

Histological examination revealed nothing abnormal in the lungs, liver, heart, spleen or intestines. Pancreas showed slight intra- and perilobular cirhosis. Adrenals showed the customary degeneration of the inner cortical zone with hyperemia.

Right kidney with low power is easily separated into an outer spongy zone and the more solid medulla. In the cortex the tubules are lined with swollen granular ragged epithelium, resembling normal convoluted tubules; the cells however are granular, and in some places filled with large "colloid" droplets. The lumen frequently contains granular material. Between these are greatly dilated tubules or cysts whose walls are lined by a single layer of more or less flattened cuboidal epithelium. In addition there are scattered small tubules resembling the Henle loops. The glomeruli are mostly well-formed, but in the superficial portion, occasional rudimentary glomeruli of small size and with the tuft covered by cuboidal epithelium may be found. In the medulla the tubules are extremely irregular in shape and caliber. They are lined by cylindrical epithelium of the usual type with distinct cuticular border. In some of the pyramids, the tubules are widely separated by a very cellular connective tissue of loose texture; scattered through this are occasional groups of round cells, and eosinophiles; some of the former are undergoing mitosis, the appearance suggesting active blood formation. The left kidney presents a similar, though somewhat more complicated structure. Distinction between cortex and medulla is not clear cut. The capsule is thickened and contains smooth muscle fibers; in several sections are small tumor like masses, lying partly within the capsule and composed of polygonal cells filled with fat globules of varying size, which are not anisotropic and stain bright red with Scharlach R. These are evidently small lipomatous tumors and not aberrant adrenals. The cortex shows a structure resembling that of the other kidney. The cyst-like spaces reach a large size. They frequently show heaping up of cells at some portion of the lining, or a spur formation resembling incomplete septa. The medulla also resembles that of the other kidney. Some of the pyramids appear to contain more numerous tubules than others; where the tubules are few, they show marked dilatation.

Scattered through both kidneys, but more numerous in the left, are islands of embryonic cartilage. They lie immediately beneath the capsule, also along the large vessels entering the hilus, and in various parts of the cortex. They are surrounded by concentric layers of connective tissue cells, and are quite sharply demarcated from the surrounding kidney tissue.

Sections through the left ureter shows a pelvic branching into two short arms. As has been said there is no dilatation into a true pelvic cavity, and the end is surrounded by a thick mass of tissue composed of smooth muscle fibers and connective tissue which appears to separate it from the kidney tissue proper. Failure of the collecting tubules to unite with the pelvis immediately suggests itself as a possible explanation for the malformation of the renal tissue. In some sections, a direct connection can be demonstrated between the collecting tubules and the rudimentary pelvic cavity; but many of the papillæ seem to be closed at the apices by a circumferentially disposed stratum of fibrous tissue, and it is the tubules in these papillæ which apparently show the greatest distention. The cavity of the rudimentary pelvis and its continuation into the ureteral lumen is lined by squamous epithelium of normal type but varying greatly in thickness in different regions; in some places there is a localized heaping up of cells.

Blood vessels show no especial change; there is a rich capillary supply to the young connective tissue which constitutes the bulk of the pyramids.

The literature contains reference to a number of cases similar to this. Aschoff[1] refers to the condition in his text as "Hypoplastische Zystenniere," and cases have been reported by v. Mutach,[4] Rückert,[6] Busse,[2] Meyer,[3] Natanson[5] and others.

The kidneys are considerably smaller than the normal.

	Right	*Left*
Measurements (after hardening) . . .	20x7x5 mm.	25x10x10 mm.
Average measurements (Vierordt)	50x24x17 "	49x25x17 "
Weights (after hardening)	0.65 gms.	1.70 gms.
Average weights (Vierordt)	10.5	

Cartilage is not uncommon in the teratomatous tumors of the kidney, but in the reported cases these are large tumore showing rapid and malignant growth with tendency to metastasize. Aside from the cartilage there is nothing in this case to justify a belief in the teratomatous nature of these kidneys, especially since the histological elements and characteristically the striated muscle fibers, of renal mixed tumors are wanting. The presence of the cartilage, on the other hand, is hard to explain. Of the possible sources, first the inclusion of aberrant skeletal tissue, and secondly a metaplasia of the young connective tissue, the latter seems more probable; but there is no real basis for decision.

In regard to the cystic structures, Virchow's original idea that the cysts were sequellæ of inflammatory conditions of the papilla, or obstruction by uric acid deposits has been generally abandoned. Evidence of inflammation in the papillæ is not found and the frequent association of other developmental anomalies, as absence of the seminal vesicles in this case, points to congenital rather than acquired causation. Of the theories which explain cysts as neoplasms and those which attribute the cysts to a failure of union of the component parts of the urinary system, the latter appears more plausible, and is more generally held. The study of this case has led to the tentative conclusion that there has been a defective connection between uriniferous tubule and ureter; the exact situation of the defect, whether down in the papillæ as would seem evident from some portions and in contradiction to the current conception, or where the collecting tubule begins we have as yet been unable to decide.

A more complete description will be published later.

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[5] Natanson: *Wiener Kl. Wochenschrift*, 1903, S. 857.

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[7] Vierordt: *Daten u. Tabellen für Mediziner, dritte Auflage.*

Discussion.

Dr. F. C. Wood said that he could not add anything new to the discussion of this case as he had never seen a specimen of exactly this type. He was under the impression that in the ordinary congenital cystic kidney the whole tissue was much more spongy than was shown in this specimen. The fact that the cystic change was not very extensive would give a wonderful opportunity to Dr. Mount to ascertain the exact site of the obstruction.

Dr. MacCallum: There are several well-known types of congenital cystic kidney. In those of which Dr. Wood spoke one can make out relatively little because of the great distortions. Others found at birth show somewhat simplified conditions. I had at one time a reconstruction made by Dr. F. M. Meader of a cystic kidney found in a newborn infant which was otherwise much malformed, with cysts of the liver and supernumery digits. In this instance the kidneys were large, soft and gelatinous, containing small cysts and were of such size that they had to be removed before the child could be delivered. It seemed possible to make out cysts connected with glomeruli and others connected with the conducting tubules.

Since that time I have seen a number of examples of another type of which fusiform cysts were found in the pyramids without any evidence of obstruction at any point. This condition is sometimes seen in the adult.

Of course the most plausible idea of the origin of the cystic kidney is that the two portions of the tubules which ordinarily unite are prevented from doing so. In Dr. Mount's case, however, there seems to be a different point of obstruction, namely between the ureteral anlage and that of the tubules.

Dr. Mount: The appearance of the kidney was as if the ureter had stopped at the pelvis and had not given off secondary branches to unite with the collecting tubules.

ADRENAL HEMORRHAGE IN A CHILD.

A. M. PAPPENHEIMER, M.D.

The subject of this report was a previously healthy, handsome, well-nourished boy of three years, who was born and lived at the Nursery and Child's Hospital. I am indebted to Dr. Freeman for the clinical history, and to Dr. Sawyer, the House Physician, for additional notes.

On the evening of April 29th, the child had gone to bed, apparently in perfect health. At 2:30 in the morning the house physician was called, and found him vomiting, irritable and delirious, with a temperature of 103°. In the morning he was again summoned because the child was having convulsions. A mustard bath was given, after which the child lay in an apathetic, semi-conscious state until its death at 12 o'clock, nine and a half hours after the onset of the symptoms. It was slightly cyanosed; the respiration became slow and gasping; the pulse was somewhat rapid, but fairly strong until a short time before death, when it failed to respond to injections of ether and camphor.

The autopsy was made the following morning. The body was that of a large, very well-nourished child, of neither pasty nor obese habitus. There were a few scattered purplish petechial spots over the trunk and extremities, and more numerous small bright red hemorhagic blotches in the visceral and parietal peritoneum. Eyes, ears, nose and teeth were normal. The thymus was large, fleshy and lobulated, and weighed 19 gms. The heart seemed relatively large, and there was a distinct hypertrophy of the left ventricle. On the aortic surface of the anterior mitral leaflet were a few atheromatous patches, and the aorta above the sinuses seemed slightly thickened. There were no other cardiac lesions or anomalies. The lungs, aside from moderate congestion and œdema, were normal. The liver was rather opaque and friable, but otherwise unchanged. The spleen was slightly enlarged, firm, dark and smooth on section. The follicles were very numerous, of moderate size, not prominent above the surface.

There was an excessive lymphoid hyperplasia throughout.

Tonsils and lingual follicles were large. In the small gut, the solitary follicles and the Peyer's plaques were exceedingly conspicous as was the lymphoid tissue of the appendix. Aside from slight hyperæmia of some of the Peyer's plaques, and for the presence of scattered punctate hemorrhages in the mucosa of the stomach and small intestine, the alimentary tract was normal throughout. The intestinal contents consisted of loose yellow fecal matter with a slight admixture of mucus. The mesenteric lymph-nodes were extremely large, up to 2 cm. in length. Most of the glands were pale and firm, a few showed central areas of hemorrhagic softening. The kidneys were pale, with injected blood vessels. The brain was large, dry and congested. The ears contained no exudate. The lesions of chief interest were those found in the adrenals. The cellular tissue about the glands was noticeably œdematous. The adrenals themselves were of normal size and shape, but on section, both glands showed a diffuse hemorrhagic infiltration, and were of a uniform dark red color. The demarcation between cortex and medulla was, however, still obvious in certain portions. There had been no extravasation into the surrounding cellular tissue.

The microscopic sections show that the diffuse hemorrhage into both glands has led to a complete destruction of the medullæ. Only a few scattered chromaffin cells are found, and for the most part, the medullary area is occupied by a closely-packed blood mass in which no other cellular elements are present. The architecture of the cortex is better preserved. The capillary walls are in places still recognizable. Between the capillaries and surrounded by red-cells, lie the cortical elements. Many of the cells still have a well-stained nucleus and a fringe of vacuolated cytoplasm. Others show pycnosis and even fragmentation of the nucleus. The columnar alignment of the cells in a few places, beneath the capsule and about the central vein, is still preserved.

The capillaries are most often collapsed; their wall seems somewhat thickened, but the nuclei of the endothelial cells are not swollen. In some of the capillaries are small groups of polynuclear leucocytes, in others hyaline thrombi. Some of the larger veins contain platelet thrombi, which for the most part do not obstruct the lumnia completely.

The hemorrhage is practically limited to the glands, but in one block, there is found a small rupture through the capsule into the adjacent tissue.

It is interesting that the extra-cortical adenomata, several of which were found in the sections examined, are entirely free from hemorrhage. They are of considerable size, and their presence in an uninjured condition might perhaps justify one in the inference that an insufficiency of cortical tissue was not the cause of death.

The nerves and sympathetic ganglia about the glands appear normal. There is an abundant exudation of fibrin forming a more or less continuous sheet about the glands.

The histological study of the remaining organs showed some features which deserve mention. The centers of the lymphoid follicles in the spleen, intestines and certain lymph-glands are composed of large phagocytic cells filled with chromatin fragments, apparently derived from fragmented, pycnotic lymphoid cells. The lesion resembles that described by Flexner in his study of lympho-clytoxins, and is a familiar one. In the liver, however, an interesting observation was made. The liver capillaries contain numerous, dark staining bodies, varying in size from that of a liver-cell nucleus to small coccus-like particles. These are undoubtedly free nuclear structures in various stages of degeneration. The larger bodies are crescentic in shape; the chromatin is condensed against the nuclear membrane, the central portion being pale. How is the presence of these degenerating nuclear particles to be explained? Obviously, they are not derived from the liver elements themselves, since the hepatic cells and the capillary endothelium show no degenerative changes. Possibly they are derived from the fragmented and pycnotic nuclei which are found in the lymphoid follicles of the intestine and mesenteric glands, and which have been swept into the liver.

In the myocardium, there were found, scattered through the musculature, small collections of polynuclear leucocytes. A distinct necrosis of the muscle fibers in these areas could not be made out.

The kidneys show an intense degeneration of the cells of the convoluted tubules. Some of the cells appear to have undergone actual necrosis; all of them are granular, swollen and stain intensely with eosin.

The cause of this fulminating illness is obscure and mysterious. Cultures made from the spleen on plain and serum agar remained sterile after four days, and we have no basis for grouping the case with any of the known infections.

The numerous cases of adrenal hemorrhage which have been reported fall into several groups. One of these groups includes the large number of cases observed in still-born or new-born infants, in which birth-trauma or manipulations to start respirations may be regarded as initiating the hemorrhage. The great fragility and hyperæmia of the inner cortical zone, which begins its regressive changes at this period, may be looked upon as contributory. In other cases of this group, the adrenal hemorrhage may be part of a general hemorrhagic infection or diathesis. Cases of this sort have been presented to the Society at various times by Prudden, Hodenpyl and Norris.

The cases occuring in adult life have been frequently associated with thrombosis of the adrenal veins, or of the inferior vena cava; trauma during abdominal operations is also an occasional cause. In still other cases of so called adrenal apoplexy, no definite cause can be discovered. Large blood cysts forming palable tumors, may be formed, and since the lesion is not always bilateral, recovery after operation is possible.

There is, however, a group of cases, closely resembling the one here reported in their clinical course and pathology, in which without previous history of infection or other illness, a child suddenly becomes extremly ill, with high temperature, vomiting, diarrhœa, prostration and convulsions, and dies within one or two days. Often a purpuric rash of greater or lesser intensity develops. Cases of this sort have been reported by Batten,[1] Andrews,[2] Voelker,[3] Langmead,[4] Waterhouse[5] and others. The autopsy reveals a diffuse hemorhage into both adrenals, with scattered hemorrhages elsewhere. Cultures from the blood, spleen and from the adrenals themselves, when these have been made, have usually been sterile, although Riesman has reported several cases in which staphylococci were recovered post-mortem, and other pyogenic bacteria have occasionally been found. In the majority of cases, the etiology is obscure. The fact that similar lesions may be produced in animals by the injection of diphtheria-toxin and other poisons of bacterial origin, suggests the possibility that these cases, in spite of their striking clinical and pathological similarity, are not necesarily all due to the same toxic or infectious agent.

In reviewing the history of these cases, moreover, it is not easy to know which symptoms are attributable to the hypothetical intoxication or infection, which we must assume to be the cause of the adrenal hemorrhage, and which to the destruction of the adrenals. We know from animal experiments, that double extirpation is regularly followed by death, the fatal outcome being delayed only in those animals such as rats, in which there is an abundance of accessory adrenal tissue. The animals die with symptoms of extreme asthenia, motor weakness and subnormal temperature. There can be no doubt that an extensive destruction of the adrenals, as in the case here described, is amply sufficient to cause death. Materna,[6] however, has suggested that the symptoms produced are rather those of an acute adrenalian intoxication, than an acute insufficiency, believing that with the hemorrhage, a toxic amount of adrenalin, or of the physiological equivalent, is swept into the circulation. With the blood serum from a fatal case, he obtained a positive Vulpian reaction and a positive frog's eye test. Although we no longer consider these tests as altogether specific, some support for this idea is found in the clinical history of initial delirium, excitement, vomiting and convulsions, symptoms which are produced in animals by the subcutaneous injection of toxic doses of adrenalin. The preservation of a strong pulse until just before death also suggests the presence of a pressor substance in the blood.

What role the sudden destruction of the cortex plays in the production of the symptoms, is, of course, entirely problematical. The presence of a considerable amount of uninjured cortical tissue in the form of extra-capsular, adenomatous masses, did not in this case, suffice to ward off the fatal outcome.

It would seem that a careful study of these cases, clinically and bacteriologically, would be of great interest. Because of the uniformity in the clinical and pathological findings, it does not seem improbable that we are dealing with a specific disease of unknown origin. Moreover a careful examination with modern clinical and laboratory methods, might throw light on some of the many problems of adrenal physiology.

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[3]Voelcker: *Reg. Rep., Middlesex Hosp.*, 1898, p. 274.
[4]Langmead: *Lancet*, May 28, 1904, p. 1496.
[5]Waterhouse: *Lancet*, 1911, Mar. 4th.
[6]Materna: *Ziegler's Beitr.*, Bd. 48, Hft. 2, S. 236.

Discussion.

Dr. C. Field: Dr. Pappenheimer's case is very interesting. Adrenals exactly similar to these of Dr. Pappenheimer's are seen not only in children as a result of diphtheria, but are a constant finding in animals dying from a lethal dose of diphtheria toxin. I have also come across similar lesions in ricin poisoning. In one case a kid injected with a large amount of diphtheria toxin and killed four hours later by bleeding, showed a tremendous hemorrhagic condition of the right adrenal, the toxin being injected in the right hind leg, the right adrenal being three times as large as the left. An especially interesting point in Dr. Pappenheimer's case is that he found small hemorrhages in the stomach and intestines, which is also a fairly constant condition in death from diphtheria toxin and ricin toxin.

Dr. MacCallum: Two possibilities suggest themselves in this case. I have asked Dr. Pappenheimer whether the child may have had diphtheria, because such hemorrhages occur in the course of diphtheria. The other etiological factor which we saw illustrated in a recent case is the mechanical injury to the adrenals. In that instance, a woman who had been operated on for an umbilical hernia showed an extensive hemorrhage in the medulla of the adrenal.

CARCINOMATOUS CYST OF PANCREAS.

J. GARDNER HOPKINS, M.D.

The specimen presented was obtained at autopsy on the body of a man aged seventy-six years. His past history was negative. Up to five weeks before death he had been apparently in good health, but at that time his family noticed that he was becoming jaundiced. He had for some time before this been very slowly losing weight, but about this time the loss of weight became more rapid, although its extent was unknown. On admission to the hospital, three weeks later, he was intensely jaundiced, quite weak, and apathetic. He complained of an indefinite dragging sensation in the region of the stomach, but presented no other symptoms. On examination he was markedly emaciated, and there was slight tenderness in the right hypochondrium. The examination was otherwise negative. His stools were acholic. His blood showed a moderate anæmia of the secondary type. His asthenia became more marked and a few days before death there was a slight rise of temperature to 100 or 100.5°. Three days before death sugar appeared in the urine for the first time. The clinical diagnosis was carcinoma of the head of the pancreas or of the gall-ducts. At autopsy a large thin-walled cyst, about 7 cm. in diameter was found lying posterior to the descending portion of the duodenum to the right of the head of the pancreas. It was filled with chocolate colored turbid fluid. This contained changed blood and a diastatic ferment.

The cyst wall was about 1 to 2 mm. thick, and the lining was smooth except at the point where it was attached to the pancreas. Here it was puckered and raised into minute papillæ. Between these was a small opening through which a probe could be passed for some distance into the pancreas, evidently following an accessory duct. The tissue at this point was quite firm, but there was no appreciable tumor mass. The pancreas itself was almost completely replaced by fat. The duct of Wirsung was dilated throughout its extent to a diameter of about 3 mm., and immediately surrounding it were some grayish patches of pancreatic tissue. The peripheral portions of the gland were entirely replaced by yellow fat in which were some areas of fat necrosis. Although the duct was dilated, as if from obstruction, a probe could be readily passed through the papillæ into the duodenum. The common bile duct was enormously dilated to a diameter of 2 cm., as was also the cystic duct. The walls were thin and of a deep green color. After the organs had been removed a probe was passed readily from the common duct into the duodenum so that the obstruction was due apparently to pressure of the cyst, which lay directly behind the papilla. The liver was deep olive green and on section small drops of pus exuded from dilated bile ducts in various portions of the organ. The other organs showed little of note. There was a small area of bronchopneumonia which may have been the immediate cause of death.

On section through the cyst wall where it was attached to the pancreas, the lining consisted of from two to six layers of flattened epithelial cells with small deeply staining nuclei. Immediately adjacent to this was a mass of dense fibrous tissue, poor in nuclei, in which there were no remnants of pancreatic acini but numerous islands of Langerhans. Some of these showed areas of mucoid degeneration, but the remaining cells stained well and appeared normal. Scattered through the fibrous tissue were small groups of epithelial cells, rarely more than six to eight in a group. Many of these cells were large and contained very large nuclei, consisting of a ring of densely staining chromatin with one or two nucleoli in the center. These cells were seen to live in the sclerotic walls of some of the vessels. Sections through the body of the pancreas showed a very few remaining acini of glandular cells which showed little evidence of post-mortem digestion. No islands of Langerhans were found in this portion of the gland. The epithelium of the dilated duct of Wirsung was in places thrown up in papillæ, in other places completely desquamated. In sections of the liver the cells about the smaller bile ducts were crowded with yellow pigment. About the larger ducts there were wide areas of necrosis and in the necrotic areas there were masses of pus cells.

The case must be considered either as a carcinoma developing in the wall of a benign pancreatic cyst, or as due to compression of the ducts by a malignant growth. The neoplasm was so very small in extent that it seemed probable that it was secondary to the cyst formation. The biliary and pancreatic obstructions were apparently due not to the neoplasm but to compression of the ducts by the cyst.

Discussion.

DR. EWING: A moment's glance at the sections in this case inclines one to believe that the process is a carcinoma.

THE RELATION OF EXPERIMENTAL ANÆMIA TO PERNICIOUS ANÆMIA.

E. E. BUTTERFIELD, M.D.

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I think most of us are agreed on one point at least in experimental medicine, that is, that the results of animal experimentation are at the best only an approximation of the conditions encountered in human pathology. It is, therefore, safe to state in the beginning that an experimental pernicious anæmia corresponding in symptoms, course, and pathological anatomy to progressive pernicious anæmia of human pathology is as yet far from realization. What, then, has been the utilizable yield of the large amount of experimental work on anæmia, which has accumulated within the last 30 years? Let us take up this work briefly in its relation to some of the problems of pernicious anæmia.

As early as 1890 it was known that erythroblasts were to be found in the spleen of guinea-pigs and cats after bleeding. Shortly afterward the same observation was made in the toxic anæmias. The significance of these observations was first brought home to clinicians and pathologists when descriptions of myeloid tissue in the spleen and liver of man in severe anæmias began to appear in the literature. Numerous valuable contributions along this line in human pathology appeared from 1900 on. The most comprehensive was that of Meyer and Heineke,[1] in which the great similarity between the mode of hæmatogenesis as well as between the types of blood-cells in the fœtus and in pernicious anæmia was duly emphasized. An additional analogy was established, the existence of a high color-index in fœtal blood.[2] At the suggestion of Meyer and Heineke, Morris[3] and v. Domarus[4] studied the anæmia produced in rabbits by phenylhydrazin derivatives and obtained severe anæmias of long duration, which had many features in common with human pernicious anæmia. These features were foci of myeloid tissue in the spleen and liver, normoblasts, red corpuscles with granular basophilia, and occasional myelocytes in the circulating blood. These phenomena were interpreted simply as evidence of blood-regeneration. Morawitz and Blumenthal,[5] Itami,[6] and Ritz[7] objected to this interpretation on the ground that they found essential differences between the toxic and post-hæmorrhagic anæmias. According to them the animals with toxic anæmia regenerated more rapidly and developed more constantly extramedullary foci of myeloid tissue. Itami believed that the extramedullary myeloid tissue was not a manifestation of simple regeneration, but developed in response to some more definite chemical stimulus. In a parallel series of experiments on post-hæmorrhagic anæmia, in which one set of animals received injections of laked blood he found more active regeneration in that set and came to the conclusion that some constituent of the disintegrated red corpuscles furnished the necessary stimulus to regeneration. Serum seemed to be without effect. Itami expressed doubt as to whether myelo- and erythropœsis in the spleen would ever be produced by repeated blood-letting alone. By alternately bleeding rabbits to the point of severe anæmia and then letting them recover, Skornjakoff[8] then proved that myeloid foci could be produced constantly in the spleen, less frequently in the liver; normoblasts in large numbers, red corpuscles with granular basophilia, and myelocytes occurred at times in the circulating blood. The only remaining difference then between the post-hæmorrhagic and the toxic anæmias would be in the rapidity and constancy with which these characteristic changes could be produced. Most recently Milne* has shown that even this difference does not exist. Repeated small bleedings in rabbits are followed promptly by the appearance of erythroblasts and red corpuscles with granular basophilia. Dr. Milne has also produced more extensive areas of myeloid tissue in the liver than have been described heretofore in any of the experimental anæmias. This would seem to restore the validity of the interpretation first advanced: a simple regeneration is sufficient to explain the picture found in the blood-forming organs in pernicious anæmia and in the experimental anæmias.

Quite apart in scope and purpose from the work just considered there is another group of experiments on toxic anæmia, which arose from observations on the bothriocephalus anæmia. It will be remembered that after Tallquist[9] had produced anæmia experimentally with a hæmolytic substance obtained from the proglottids of Bothriocephalus latus, Faust and Tallquist[10] succeeded in isolating and identifying the hæmolytic agent as the cholesterin ester of oleic acid. In their feeding experiments they found that this substance was split into cholesterin and oleic acid in the intestine and was resorbed in the chyle as oleic acid or

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*Unpublished work, to appear in *Journal of Experimental Medicine*, Vol. 16, p. 325. I am very much indebted to Dr. Milne for the privilege of drawing freely on his unpublished results to-night. This work rounds out fairly completely the picture of protracted post-hæmorrhagic anæmia in rabbits and establishes more clearly than any previous work the analogy between this condition and pernicious anæmia of human pathology.

Na-oleate. The chyle became strongly hæmolytic. The presence of such a high percentage of free acid or soap in the chyle resorption of oleic acid from the intestine is quite out of harmony with the prevalent and apparently well established views on the resorption of fats. This discrepancy has not yet been cleared up. Recently H. M. Adler[11] has studied the anæmia produced in rabbits by olive oil and oleic acid and embodied his results in a paper entitled "experimental pernicious anæmia." According to the descriptions, however, neither the blood picture, nor the course, nor the pathological anatomy resembles pernicious anæmia any more or even as much as do the acute anæmias produced by the phenylhydrazin derivatives. On the whole, therefore, it cannot be said that the experiments with substances isolated from the Bothriocephalus have been as successful in imitating the blood-picture and pathological anatomy of pernicious anæmia as has been the experimental work on post-hæmorrhagic anæmia.

I have purposely made no reference to a high color-index in the experimental anæmias, for, it seems to me that proof is lacking that this almost pathognomonic symptom of pernicious anæmia has been successfully imitated in the experimental anæmias. On looking over Tallquist's figures one finds that his apparently high indices are with one exception due solely to his manner of calculation.

Let us now turn to some more general features of severe anæmias. In 1909 Boggs and Morris[12] called attention to the occurrence of lipæmia in the post-hæmorrhage anæmia of rabbits. This occured quite constantly and became marked when the red corpuscles fell below 2,000,000. From the milky serum they isolated 2% to 4% of an oily substance which gave very high figures for iodine absorption although it did not reduce osmium tetroxide. In accordance with the work of Cohnstein and Michaelis[13] the first assumption would be that the organism was unable to oxidize its fat on account of the reduction in the number of red blood corpuscles. It will be recalled that Cohnstein and Michaelis showed that for the disappearance of chyle-fat from the serum, red blood corpuscles or laked blood and oxygen were necessary. Serum alone was without effect. The explanation is somewhat shaken by the fact that in the toxic anæmias with the same reduction in the number of red blood corpuscles and hæmoglobin lipæmia did not occur (Boggs and Morris). This may constitute an essential difference between the toxic and the post-hæmorrhagic anæmias.

The nitrogen metabolism in anæmia has long been a subject for discussion.[14] It was claimed at first that there was a daily loss of nitrogen following repeated blood-letting. This seemed to be overthrown when Van Noorden[15] found a marked nitrogen retention instead of a deficit in pernicious anæmia. On looking over Van Noorden's cases it will be found that the metabolism was studied during periods of regeneration and it is therefore to be expected that the nitrogen balance would be positive. In a disease of such a remittent course it is necessary to have long series of determinations carried through the periods of blood destruction as well as regeneration. In fact Rosenquest[16] found great irregularity in the nitrogen balance in pernicious anæmia, although a definite relation to the condition of the blood was not apparent. Although metabolism experiments in the experimental anæmias, toxic and post-hæmorrhagic, would go far toward clearing up the apparently contradictory views, trustworthy results have not yet been forthcoming. Some general observations have been made in the post-hæmorrhagic anæmias which may indicate roughly what is going on. In the first week of the anæmia after from 80 to 100 ccm. of blood have been withdrawn there is regularly loss of weight amounting to 300-400 grams, that is 1/6 to 1/5 of the initial weight.[17] When the bleedings are pushed further the loss of weight continues and if the animals are killed after a period of protracted sustained anæmia there is an almost complete disappearance of subcutaneous and abdominal fat.[18] Associated with this there is fatty change and hæmosiderosis* of the organs with central necrosis in the liver. It is quite evident that there is a profound disturbance of nutrition in a sustained post-hæmorrhagic anæmia. On the other hand, if the animals are allowed to recover the body weight rises and after a period of regeneration may surpass the initial figure. In Skornjakoff's experiments on post-hæmorrhagic anæmia of 5 to 6 months duration with alternating periods of severe anæmia and regeneration the body weight of the animals during the last period of regeneration was about the same as at the commencement of the work. Over a liter of blood was withdrawn in one of these experiments.

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*It is difficult to conceive why such marked hæmosiderosis should occur in post-hæmorrhagic anæmia. Morawitz assumed that the newly formed red blood corpuscles were less resistant than the normal ones. Direct determinations, however, have shown that the resistance to hypotonic solutions is not diminished (Milne).

In summing up: The one fact which stands out clearly as a result of the work on post-hæmorhagic anæmia is the almost complete analogy between this condition and pernicious anæmia in the changes in the blood and blood-forming organs. This demonstrates that these changes may be interpreted with reasonable certainty as phenomena of regeneration pure and simple. The prompt appearance of red blood corpuscles with granular basophilia following withdrawal of a few ccm. of blood proves conclusively that this granulation is not a result of cytoplasmic degeneration but is an accompaniment of regeneration. Concerning many other problems intimately connected with pernicious anæmia, for example, the question of autochthonous formation of myeloid tissue in the spleen and liver, the genetic relations between the different types of blood cells, the nitrogen balance in different phases of severe anæmia, and the mechanism by which compensation for the diminution in the oxygen carrying power of the blood is effected, the experimental work has as yet yielded no unequivocal results. In fact the positive knowledge which we possess concerning these questions is still almost exclusively the result of clinical, pathological anatomical, and embryological investigation.

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Discussion.

Dr. Ewing: The work on experimental anæmia has doubtless been of great service in showing what features of the disease in man may be referable to hæmorrhage and some other forms of blood destruction and it has been a pleasure to listen to Dr. Butterfield's able summary of this work. I agree however with Dr. Wood that the true picture of progressive anæmia of man has not been produced experimentally; and I doubt if it can be.

The experimenters have used chiefly blood letting and various hemolytic agents to produce the disease. Yet it is well known that pernicious anæmia in man rarely follows hæmorrhage.

The human being can tolerate many large hæmorrhages and small bleedings frequently repeated over long intervals without developing a progressive fatal anæmia. Likewise there is no adequate evidence to show that any poison is essentially concerned in the genesis of cryptogenic pernicious anæmia. The etiology is quite complex but one important factor which the experimenters overlook is the congenital tissue predisposition which renders certain rather rare human beings susceptible to the disease.

It has never appeared certain that the experimental animals possess this peculiar susceptibility. I have long felt that the essential features of Biermer's anæmia is its progressive fatal tendency and that the tendency depends upon the establishment of an abnormal type of blood production in the bone marrow. The mysterious factor in this change has, I think, not been revealed by the experimental studies.

Dr. F. C. Wood said that Dr. Butterfield's discussion was very interesting. The experimental animal usually chosen was rather unsatisfactory for such work. About 1898 or 1899 he had done some work on the experimental production of so-called pernicious anæmia by the injection of pyrodin, phenyl-hydrazin, etc., using the rabbit, but after a considerable series of experiments had given up the attempt to produce a true pernicious anæmia. Several writers had published statements that by these substances they had produced pernicious anæmia, but Dr. Wood had never been convinced from their reports that the type of anæmia produced was the form which we call pernicious anæmia. It should also be remembered that the true Biermer anæmia is a very different type from the anæmias produced by hemolytic agents in human beings.

Dr. Butterfield: It would seem that different animals regenerate much more rapidly and completely than others. In dogs, for instance, it is quite difficult to produce a severe anæmia, even after repeated withdrawal of large quantities of blood.

As to whether pernicious anæmia is to be interpreted as a manifestation of defective hæmatogenesis or rather as a disease characterized by alternating periods of hæmolysis and regeneration, it seems to me that there is no absolute proof of either view. The strongest argument in favor of the interpretation as a hæmolytic-regenerative process is the fact, that it is possible to imitate roughly in animals the essential pathological anatomical features of pernicious anæmia by chemicals which cause hæmolysis and by repeated blood-letting. The fact that the type of hæmatogenesis in pernicious anæmia differs quantitatively, it is true, but not qualitatively from normal post-fœtal hæmatogensis and the similarity between the blood-forming organs of the fœtus and the same organs in pernicious anæmia may be and have both been used in support of either view. The occurrence of marked hæmosiderosis in pernicious anæmia points strongly to a primary hæmolysis, especially when correlated with the bothriocephalus anæmia. But it is exactly here that the study of experimental anæmias warns us against drawing hastily the obvious conclusion, for, as already mentioned, intense hæmosiderosis occurs frequently in experimental post-hæmorrhagic anæmia accompanied with regeneration.

PNEUMONIA DUE TO POISONING BY NITROGEN TETROXIDE.

F. C. WOOD, M.D.

When nitric acid acts upon certain metals, such as copper, silver, cadmium, etc., a gas is given off which is composed chiefly of nitrogen dioxide (NO). When this comes into contact with the air it absorbs oxygen with the production of nitrogen tetroxide (NO_2)) which is easily visible because of its brownish color. The same reaction as regards the end products occurs when nitric acid acts on organic material. While the inhalation of small quantities of these gases causes no serious discomfort, if the mixture is concentrated or if it is inhaled for a sufficient time, serious and even fatal results occur. Strange to say, however, although there are on record over 250 deaths from the inhalation of these fumes, and many more cases must be unpublished, yet there are only a very few reports of autopsies, and still fewer of the careful microscopical study of the tissues. It may not be without interest, therefore, to show the lesions in the lung of a patient dying of this poison and also the alterations produced in the lungs of dogs by the inhalation of nitrogen tetroxide.

The clinical history of the patient was obscure, but the facts obtained were as follows: He inhaled the fumes from a vessel containing large quantities of nitric acid and what was probably a cadmium silver alloy. The patient felt a sensation of choking and ran to the open air; a few moments later he vomited, and then felt much better, ate a heavy dinner, and was free from symptoms until about six hours after the accident, when he was seized with intense dyspnœa and collapsed. He was taken to the hospital and died seven days after the inhalation. The symptoms were chiefly a most intense dysœna, and pain in the throat and chest; occasionally there was a moderate amount of coughing but this was not a prominent symptom. Physical examination showed an irregular consolidation at the bases of both lungs posteriorly. During his stay in the hospital his temperature ran from 100 to 102; respirations from 44 to 60; pulse from 100 to 140. Methemoglobin could not be demonstrated in the blood. At autopsy the chief lesions were a moderately dense lobular pneumonia in the lower and posterior portions of the lungs on both sides and an irregular cavity containing clear fluid and with sharply defined walls in the corpus striatum on each side of the brain. Microscopical examination of the brain lesion showed that the appearance was probably due to an artefact, produced by pressure of the embalming fluid, as the walls of the cavity were perfectly sharp with unaltered nerve cells and fibers up to the edge. The lesion in the lung was most interesting. It assumed the general type of a lobular pneumonia with very marked emphysema between the consolidated areas. The lesion was, however, very irregular in type. The alveoli in some places were filled with blood corpuscles, in others with a fibrinous meshwork, in others with large phagocytic cells containing much blood pigment, in others with masses of desquamated alveolar epithelium, and finally in a few there were plugs of regenerating epithelium. Portions of the lung had completely collapsed and the alveolar walls had undergone considearble thickening so that the lung was carneous. No bacteria could be found by staining.

The picture was so peculiar that a large series of experiments were carried out on animals to determine whether it was possible to imitate this lesion. This was found to be perfectly practicable in dogs. The lesions produced by the inhalation of vapors from a vessel containing nitric acid and copper were extremely severe in animals, and it was somewhat difficult to regulate the dose so as not to cause death within a few minutes from an acute œdema. Those animals which breathed a very dilute mixture or had only a single deep breath of the concentrated gas, survived, and often recovered entirely. For two or three days the animals suffered a good deal of dyspnœa with frequent coughing up of frothy mucus. After four or five days the animals usually improved, though some remained feeble and sick for some time longer. Microscopical examination of the lungs at different stages showed after twenty-four hours an acute exudative inflammation with much blood and serum. Later the alveolar epithelium began to regenerate; the ends of the finer bronchi were often plugged with connective tissue or cells, the appearance which has been called by Fraenkel "bronchiolitis obliterans."

In every way, then, the animal lesions were practically identical with those seen in man, if we allow for the slightly different structure and position of the dog and the human lung. Lantern demonstration followed.

Discussion.

DR. EWING: I have had opportunity to study the lungs in this case and found them highly interesting. The main feature was, as Dr. Wood describes, a remarkable desquamation of alveolar epithelium.

There were thrombi in many small vessels, and in many areas there were many heavily pigmented cells, such as are seen in the lungs of heart disease. Finally, there was, in my sections, quite a definite interstitial productive pneumonia. The characteristic lesions of the so-called bronchiolitis fibrosa obliterans, were missing. The epithelium of the larger bronchi was intact. It was difficult to reach a conclusion regarding the origin of the lesion and still more difficult to determine the exact cause of death. In this task the clinical history was not made available to me, but it was stated that the patient was in an advanced stage of chronic alcoholism. I would like to ask Dr. Wood if he observed in the lungs of his experimental animals the definite production of connective tissue and the collections of pigmented cells.

The general details of his experiments are also important, the method used in preparing the acid fumes, how close to the container the animals' nostrils were held, and how concentrated were the fumes. I performed some tentative experiments to determine the effects of inhalation of acid fumes on conscious animals, mostly guinea-pigs. I failed to produce any marked disturbance in guinea-pigs exposed to fumes of hydrochloric acid or nitric acid, under conditions reasonably simulating those to which the patient was said to have been subjected. I did not anesthetize the animals, but the fumes were so strong that tear fluid was instantly converted into foam and the animals struggled and snorted vigorously. On removal from the fumes, the animals promptly recovered and remained well.

Dr. Philips: This subject of nitric oxide poisoning is very interesting. I think in our service here in New York we rarely ever see these cases. Dr. Hudson, who has had an opportunity to see more of these cases clinically than anyone in this country, is here to-night, and I would like you to hear what he has to say.

Dr. W. G. Hudson: Dr. Hudson of the Dupont Powder Co. related some experiments which he had made with acid fumes. His conclusions based upon his experiments were as follows:

I. Injurious effects are due to the direct action of the fumes upon the lung tissues and not to changes brought about by absorption into the blood.

II. After a latent period of several hours there develops regularly, when the experimental conditions are properly arranged, an acute and usually fatal pulmonary œdema. Several animals which recovered later developed pneumonia.

III. No marked changes were found in the blood picture or in the coagulation time.

Dr. Butterfield: If I understood correctly, the fumes of nitrogen tetroxide were really inhaled in these experiments, for, of course, nitric oxide cannot exist as such in the presence of oxygen. In the presence of water HNO_3 and HNO_2 would be formed from the NO_2 gas. One would, therefore, expect to find chiefly the combined action of acid (hydrogen-ions) and nitrite. The lesions in the lungs of the animals appear to be referable chiefly to the former. If nitrite formation occurs one would expect a most characteristic change in the blood, that is the conversion of oxyhæmoglobin into methæmoglobin. In fact one of the most convenient methods of preparing methæmoglobin is to pass nitric oxide into the blood in the presence of oxygen.

A CASE OF FOREIGN BODY IN THE HEART.

C. H. BAILEY, M.D.

The organs exhibited were removed at autopsy from a patient who on entering St. Luke's Hospital gave a history of having been on a spree of five days' duration. Immediately following his dissipation he was seized with nausea and vomiting, and for five days all food taken was immediately expelled. He entered the hospital complaining of fever and muscular pains; the vomiting had ceased. His temperature ran an irregular course, ranging from 102 to 106. The white blood cell count rose from 22,000 on entrance to 34,000 two days later, with 85 per cent. polynuclears. A blood culture taken during his second day in the hospital showed *Streptococcus vividans* and *Bacillus coli communis.* The patient grew gradually worse, and died four days after entrance.

At autopsy the pericardium was found to contain 75 c.c. of unclotted blood. Protruding 1.5 cm. from the posterior tip of the right auricle was the end of an ordinary wooden toothpick. The other end could be felt within the auricle pressing against its anterior wall at the right auricular appendage. The wall of the pericardium where it was in contact with the protruding end of the toothpick was abraded but not pierced.

On the posterior wall of the duodenum, 14 cm. below the pylorus, at the point where it lay directly over the inferior vena cava, was an ulcerated area, 0.5 cm. in diameter. At the base of this ulceration there was a sinus, 1.5 cm. in length, leading backward and upward directly into the inferior vena cava. The anterior wall of the vessel in this region presented a rough eroded surface for about 5.5 cm. lengthwise of the vessel. The venous end of the sinus was closed by a small clot.

Nineteen cases in which foreign bodies were found in the heart have been reported in the literature, omitting the large number in which entrance to the heart was gained directly through the chest wall. Several of these cases gave a history of having swallowed the foreign body, but in none of them was a lesion demonstrated between the digestive tract and the venous system.

The present case appears to be unique in the demonstration of such a lesion.

The case will be reported in full elsewhere.

Discussion.

Dr. Field: In considering this case I think that particular interest lies in the fact that cultures of streptococcus viridans and B. Coli communis were found in the blood, as indicating the possible portal of entry for the viridans infection.

Dr. Bailey said that colonies of *Streptococcus viridans* were very numerous on the plates. Those of *Colon bacillus* were less numerous and it was feared that the latter might be a contamination. The autopsy findings, however, seemed to justify their presence in the cultures.

A COMPARATIVE STUDY OF THE WASSERMAN AND WEIL REACTIONS IN SYPHILIS.

CYRUS W. FIELD, M.D.

In 1906 in the *Journal of Infectious Diseases,* Weil described the occurrence of an increase in the resistence of red cells to cobra venom lysin in patients suffering from syphilis. A little later Schwartz reported on 600 cases in which he compared the Wassermann and the Weil reactions. This year Stone, of Toledo, reported another series; and Kuschucoff from Wassermann's laboratory has also reported a series.

Last spring we began a routine Weil test along with our routine Wassermann. We found that the Weil reaction was positive in 76% of primary syphilis, in 75% of secondary, in 73% of tertiary and 40% in questionable and negative cases and 50% in cases suffering from tumors, whereas the Wassermann reaction in the same series showed 70% positive in primary syphilis, 87% secondary, 75% tertiary and 30% in the questionables and negatives. These figures are almost alike except that the Wassermann reaction gives a higher percentage in the secondary cases.

It was found that there were a few cases in which we obtained a positive Weil reaction in which there was absolutely no suggestion of syphilis or malignancy and we determined to run a series on absolutely normal individuals and so obtained the blood from eighteen of the internes of Bellevue Hospital for the Weil test. In sixteen of these cases enough was obtained to control it with the Wassermann. All sixteen were negative with the Wassermann. The two on whom there was no Wassermann test were both negative with the Weil reaction. In the other sixteen cases the Weil reaction was strongly positive in one, and a doubtful positive in two, negative in all the rest. None of these three individuals have any history, signs or symptoms which would indicate a specific lesion in either their personal or family history.

From our work with the Weil reaction it would seem to be of value in known cases of syphilis undergoing treatment and possibly where the Wassermann reaction could not be readily undertaken. The test itself is of very great theoretical interest as it shows that there is a distinct difference in the chemical constitution of the erythrocytes in normal individuals and in those suffering from syphilis and new growth. I do not think that one strong positive in eighteen is a fair number of positives from non-syphilitic individuals as it will give a high percentage, which would not be found if the number of cases were greater, though I do think that it will be found that the Weil test will give a larger proportion of positive results in non-luetic conditions than does the Wassermann.

Discussion.

Dr. Weil: I feel that Dr. Field has been rather too kindly in his treatment of me. He states that the cobra venom test was positive in three out of eighteen cases, which makes the percentage of error 16%. If it is present in 16% of other conditions, then it should not be used as a diagnostic test under any conditions. I did not myself describe the resistance of cobra as diagnostic of syphilis, but as a very frequent accompaniment of syphilis. One may say that anæmia is very characteristic of late cancer, and still not maintain it to be a diagnostic sign. In fact, in my original paper, I described two "positive" reactions in individuals in whom it was gratuitous to suspect syphilis. Nevertheless, I believe such incidents to be rare exceptions to the rule that non-luetics do not react. Since my article was published in the *Journal of Infectious Diseases*, it has been taken up by several others who have attempted to show that it is almost diagnostic of syphilis, in the sense that it occurs in no other conditions. Until Dr. Field threw this bomb, I must say that I had been quite convinced by the evidence hitherto advanced.

Schwarz (*New York Medical Journal*, 1906, Jan. 6), gives a record of seventy-five cases of non-lues tested by the Weil reaction in which there was no positive reaction.

Stone, of Toledo (*Arch. Int. Med.*, July, 1912), gives a record of forty-three non-luetic cases tested, in which there was only one positive reaction.

Kuschakoff (*Ztschrft. fr. Immunitalsforsch*, XII, 5, 1912), who publishes from Wassermann's own laboratory, gives a record of from eighty to one hundred cases tested with both Weil and Wassermann reactions in which he showed that the resistance of sixty-seven undoubted luetic cases gave 15% more positives with the cobra venom test than did the Wassermann. In twenty-one controls he found one positive to cobra.

All of this evidence added together gives a record of one hundred and forty-nine cases in which lues had been excluded in which there were only two positive reactions. This result compares not unfavorably with the Wassermann, and is borne out by the further analysis of about five hundred cases, with the details of which I will not burden you, giving in all about 1.5% of error.

In summing up, I should say, as in my original paper, that the cobra test does not at present compete with the Wassermann as a reactive test. Cancer cases should be always excluded, as they may give a positive reaction due to a general resistance, not to a specific one, as after injections of phenyl-hydrazine. In treated cases, old latent cases, and scarlets, the reaction may complement the Wassermann.

From a theoretical standpoint, as a bio-chemical reaction, the resistance to cobra seems to me to be of great interest. It is not specific, in the sense of antibody antigen reactions and could hardly be expected, therefore, to be absolutely diagnostic, like a Widal. But then, it is also true that the Wassermann reaction is not specific; it does not work with cultures of spirochetes, but does with ox hearts.

Discussion.

DR. FIELD: I have already said that the percentage based on the eighteen cases obtained from the Bellevue Hospital staff was not a fair figure. We also notice that Dr. Weil's statistics are the lowest, the next highest are those of Schwarz, and then Stone, which shows that the tendency has been to raise the percentage of the positive Weil reactions and establish it as a diagnostic reaction. Kuschucoff's one positive case among his control was a case of tuberculosis with no history or sign of lues.

A STUDY OF THE MALPIGHIAN BODIES IN A CASE OF SUB-ACUTE GLOMERULO-NEPHRITIS.

SAMUEL CLARK HARVEY, M.D.

(From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York.)

The histological details of glomerulitis* and their bearing on its mode of production have been the subject of much careful investigation and of a voluminous discussion extending over considerable time. There is yet lacking, however, any concordance of opinion and much may be accomplished by the consideration of the finer details in appropriate though isolated cases and their correlation with what is already known. It is in the hope of being of some assistance in this respect that this paper is written.

It is necessary to review briefly the literature bearing upon glomerulitis in order better to appreciate the important points to be observed in the description of the case reported. For a more complete consideration one is referred to articles by Löhlein,[1] Reichel[2] and Herxheimer.[3]

Changes in the glomeruli in nephritis had been previously described by Virchow, Beer, Johnson, Forster, Frerichs and others, but to Klebs[4] belongs the credit for the first careful histological study used as the basis for an explanation as to the mode of production of the lesion. The essentials of his description are a swelling of the glomeruli, an increase in the number of cells lying within them and a lack of blood in the capillaries of the tuft. From this picture he reasoned a proliferation of connective tissue cells which are assumed to be present normally in small numbers between the vessel loops. This results in compression of the capillaries so that they no longer permit the flow of blood through the glomeruli. He also observed a slow proliferation and degeneration of the capsular epithelium but regarded this as of secondary importance to the vascular lesion.

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*The term "glomerulitis" as first applied by Cornil and Brault[5] to inflammatory changes in the Malpighian bodies is misleading, as has been pointed out by Herring.[6] From the standpoint of derivation it does not include the capsular and pericapsular lesions. However, as it has come to signify all the changes seen in and about the glomerulus, and as we have no better term, it is used with this meaning here.

The expression of this opinion immediately aroused interest in this problem and was soon followed by the publication of other papers describing various details and proposing numerous hypotheses. These may be in general divided into two main groups; the first agreeing with Klebs that the essential lesion is compression or blocking of the vascular loops; the second, maintaining that the varied aspects of glomerulitis are due to a quite direct toxic action on the various structural components of the Malpighian bodies.

Blocking of the vessels of the tuft may be brought about in one of three ways; from within, by the lodgment of emboli or the formation of thrombi; from without, by the thickening of the vessel wall; or by compression. Each of these three views has its advocates.

Thrombi in the vessels have been repeatedly observed (Langhans,[7] Councilman,[8] Klein,[9] Nauwerck[10] and many others), and the origin of these was for some time the subject of a quite animated dispute. Proliferation and desquamation of the lining endothelium (Litten,[11] Langhans,[7] Welch[12] and others), blockage with cells transported there by the circulation (Ribbert,[13] thrombotic and hyaline changes in the static blood (Langhans,[7] Nauwerck[10] and others), and the lodgment of bacterial emboli (Reichel,[2] Baehr[14] and others), are the most important of the ascribed sources for such intracapillary masses.

Changes in the wall itself which have been held sufficient to occlude the lumen are hyaline degeneration and swelling of the endothelium and of the supporting framework of the capillaries (Herxheimer,[3] Lyon[15] and others).

Compression of the tuft vessels from without is the view which has been most frequently proposed. In the main, three methods of accomplishing this have been suggested; First, nearly all writers have noticed an increase in the number of nuclei in the glomeruli. Some have considered these to indicate a proliferation of connective tissue cells (Klebs,[4] Langhans,[7] Hanseman[16] and others), other writers invading endothelial or epithelial cells (Cornil and Brault,[5] Councilman[8] and others), and still others, wandering cells from the blood. A sufficient degree of pressure may be exerted by the mere presence of a large number of cells, by the hyaline swelling and desquamation of those elements, or by the contraction of aging connective tissue.

A second method of producing pressure upon the glomerular vessels which has been suggested by several authors (Böhm,[17] Goeman[18] Tschitowitsch[19] and others), is by an increase of connective tissue about the capsule which by direct pressure or by obliteration of the afferent artery at the base of the tuft produces the changes described.

Lastly, some assume proliferation and desquamation of the epithelial cells either of the capsule or of the tuft, or of both in such quantity that a direct compression of the glomerular loops is produced (Greenfield,[20] Chapman,[21] v. Kahlden,[22] Lyon[15]).

On the other hand, several writers (Löhlein,[1] Ophuls,[23] Herringham and Thursfeld,[24] Engel,[25] Fichera and Scaffidi[26] doubt the compression of these vessels by any of these mechanisms and describe them as filled with blood and capable of normal functioning. This being true, the proliferation and desquamation of epithelium, the hyaline changes and the cellular infiltration seen in the early stages are all the direct result of a toxic influence and show a varying preponderance of type depending upon the intensity and the duration of its action.

Aside from this problem, the nature of the "crescent" has been the subject of much discussion. Litten,[11] Marchiafavi and Volenti[27], and Greenfield [28] were among the first to make a careful study of this condition. Greenfield believed it to be a proliferation of the capsular epithelium and described it as of common occurrence in subacute and chronic nephritis and also as being present in many acute cases, especially in scarlet fever. Previously Klebs,[4] Klein[9] and Kelsch,[29] as well as others, had noted these changes in the epithelium but considered them of secondary importance.

Gaylord,[30] Tschistowitsch,[19] and Engel[25] have called attention to the presence of small alveolar spaces in these bodies and the latter has suggested the following hypothesis as to the method of formation of the crescents. The toxic action causes a desquamation of epithelium which leaves denuded areas of capsule and glomerulus. These coming in contact adhere or a fibrinous exudate is formed which later becomes organized and the resulting adhesions covered with proliferating epithelial cells. He considers the entire process as strictly analogous to similar changes seen in serous cavities as described by Heinz[31] and Grasen,[32] and terms it "glomerulitis adhæsiva."

Herringham and Thursfield,[24] although they have confirmed Engel's observation question his interpretation. They believe that the different forms of these crescents represent varying stages of inflammatory exudation. The fluid having undergone solidification and containing desquamated epithelial cells, is pressed by the glomerulus into the peculiar shape observed.

The opinion that these are epithelial cells is by no means unanimous. The characterization of the lesion as a chronic or subacute condition and the observation of cases in the later stages has apparently influenced many to consider these cells as of connective tissue origin. Some difficulty has been encountered, however, in associating this idea with that of their intracapsular location and several ways have been suggested to account for this unusual position. Ziegler[33] and Recklinghausen[34] have suggested a metaplasia of epithelial into connective tissue and Böhm,[17] Goeman[18] and Tschistowitsch[19] that the membrana propria or the pericapsular tissue may send out processes. In addition to this Böhm describes actual rupture of the capsule and the subsequent invasion of the space through these gaps. Engel[25] and more recently Ophuls[23] think that these cellular masses represent but the end result of the organization of an inflammatory exudate.

Welch[12] and Lyon[15] in the acute experimental lesion produced by cantharides have seen a massing of epithelial cells in the capsular space which they believe to be desquamated and regurgitated from the first portion of the tubule. Herringham and Thursfield[24] deny that these have such a derivation.

The case described is from the medical service of Dr. Theodore C. Janeway at the Presbyterian Hospital and from the pathological service of Dr. W. G. MacCallum to both of whom I am greatly indebted for the privilege of reporting it.

Clinical History: J. C. S. Male, aged 30 years. No possible cause of nephritis was elicited. Mother died of Bright's Disease. Two months previous to admission had had trouble with his eyes and a month later was told by a physician that he had kidney trouble with a high blood pressure. Two weeks ago began to have occipital headaches and stopped work; but has suffered continuously with them since. He noticed no œdema, but a week previous to admittance passed large quantities of urine. The physical examination was practically normal, with blood pressure varying from 160 to 200 mm. Hg. Two days after admittance the phenosulphonpthalein test gave a first appearance in one hour, and a total excretion of 22% in two hours. A day later, in the evening, puffiness about the eyes was noticed and the blood pressure registered 225 mm. Hg. He had passed no urine during the day and the next morning was totally blind. A venesection was done without any improvement and he continued to grow worse, passing but little urine. The blood at this time showed 0.153% of urea. The patient died seven days after admittance to the hospital. On entrance the urine showed a heavy trace of albumen with very many granular epithelial hyaline casts and some red blood cells. The temperature was normal.

The autopsy was performed by Dr. Lamb twelve hours after death and to him I am indebted for the clinical history as well as gross description. Nothing of note was found elsewhere than in the kidneys except for a moderate hypertrophy of the heart.

Macroscopical Examination: The left kidney weighs 210 gms. It measures 11 x 5.5 x 4 cm. The capsule strips fairly easily exposing a surface showing pale reddish areas and a peppering with minute yellow specks. On one portion there is a considerable area of greenish discoloration extending a short distance beneath the surface. On section the cortex averages from 5 to 7 mm. in thickness. The striations are difficult to make out and where seen are much distorted. The same yellowish points are seen throughout the cortex and the medulla. The pelvis and ureter are normal. On closer examination the surface also shows numerous irregular gray areas. The right kidney weighs 215 gms. and measures 13 x 6 x 4 cm. It is similar in appearance in all respects to the opposite kidney except that in the pelvis there are a few minute hæmorrhagic spots.

*Microscopical Examination.**—The larger blood vessels contain a small amount of blood. Their walls are not thickened and they do not show any hyaline change. The small vessels and capillaries in general seem somewhat distended with red blood cells. The arteries at the base of the glomeruli are wide open and in many instances can be traced well inside the tuft to the point where they break up into the capillary loops. Several of these are distended with blood, even in the Malpighian bodies in which the inflammatory changes, consisting of epithelial proliferation and hyaline degeneration in the tuft and capsule, are especially well marked. In every glomerulus at least a few loops may be found in which red blood cells are in an excellent state of preservation. In general, however, the greater the hyaline change the less the amount of blood in the tuft vessels. Spaces which appear to be capillaries containing no blood are frequently seen, and in an occasional one may be found granular material or swollen cells, but no thrombotic masses are made out. That such an appearance may be caused by lymphatics or capillaries cut obliquely or longitudinally seems entirely possible if one bears in mind the difficulty with which observations are made in such a minute and complicated structure as the glomerulus.

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*The microscopical examination was made with specimens fixed in Zenker's and in formalin. Mallory's aniline blue connective tissue, Mallory's iron chloride hæmotoxylin, Van Gieson's, Sudan III, and hæmotoxylin and eosin were the stains employed. The first was found to be by far the most satisfactory, especially when the acid fuchsin was omitted, since it enabled one to follow the connective tissue and hyaline in great detail.

Too much emphasis cannot be laid upon the necessity for examining such material in serial section. The appearance at different levels in any given glomerulus may be very different and a single section often gives a quite inadequate and erroneous idea as to the changes which have taken place. This microscopical description is based upon such an examination.

The number of nuclei in the glomeruli is not increased if one is careful to rule out those epithelial cells lying between the loops and in the crevisses of the tuft. A great majority of the intraglomerular cells have large round or slightly oval nuclei in which the loose network of chromatin stains sharply. In the more hyaline of these the chromatin tends to be massed to a greater extent at the periphery of the nuclei. No mitoses are observed in these cells. The cell outline is exceedingly variable, being occasionally circular, more often oval or drawn out in a lanceolate form. The cytoplasm takes the eosin stain in some instances quite brilliantly, in others more faintly and with Sudan III, in many, droplets of fat are found. In a few glomeruli these cells appear to be fused together in hyaline masses, and here the nuclei are comparatively infrequent. An occasional polymorphonuclear leucocyte or a small round mononuclear may be found and now and then a plasma cell. However, the great majority of the cells seem to correspond to the endothelial type.

The most striking change apparent in the glomeruli is the presence of a large amount of intercellular tissue which takes an intense blue with Mallory's connective tissue stain. The substance is not at all fibrillar and seems to lie with respect to the vessel loops in the same position as the membrana propria of an epithelial membrane. With hæmotoxylin and eosin the entire intercellular substance of the glomeruli seems to stain varying degrees of red and quite intensely in many places. The cells in those tufts showing the greatest change from the normal also stain a bright red and seem to fuse with the intercellular substance so that the whole has a homogeneous appearance. Such masses of fused endothelial cells may be easily taken for hyaline thrombi in the capillaries, but no such appearance is found with Mallory's stain.

At the base of the tuft the pericapsular tissue does not seem in any considerable degree continuous with the intercellular material of the glomerulus and there is no disproportionate increase in the hyaline material at this point. The epithelial cells covering the glomerulus are supported on a hyaline membrane which resembles that lying beneath the endothelial cells of the capillaries. The connective tissue fibers passing across the capsular space with the adhesions, apparently do not invade this membrane but seem only attached to it.

The epithelial cells covering the glomerulus and dipping between the folds of it are of an irregular and somewhat flattened cuboidal type. The nuclei are large, oval and vesicular and no mitoses are observed. The cytoplasm is highly granular and in some cells large droplets staining a blue or in a few instances a bright red with Mallory's connective tissue stain are seen. With Sudan III fat droplets now and then are observed. It is only occasionally that these cells are piled upon each other and it is impossible to say whether those seen lying loose in the capsular space are of glomerular or of capsular origin. In places where there are adhesions between the capsule and the tuft the epithelium is continuous over the surface of the adhesion as far as the proliferating capsular type into which it gradually merges. In the very advanced stages of hyaline change in the glomerulus these, as well as the intraglomerular cells, are few in number and degenerating.

The capsular epithelium in a great majority of instances shows some degree of proliferation, varying from a layer two or three cells deep to the crescent shaped masses which are so characteristic of this type of kidney. These cells approximate very closely in appearance those lining the glomeruli. They are large and cuboidal in shape, slightly oval and vesicular, with a sharply staining network of chromatin. No mitoses are observed although two or three cells are seen in which two small nuclei are present, and a few others in which the chromatin is grouped in larger masses and takes the hæmatoxylin more intensely. The cytoplasm is finely granular and only in the late stages of the lesion does it show marked degeneration. It is apparently only when these cells become detached that fatty or hyaline droplets are seen within them.

When these proliferating cells form masses more than two or three layers deep a careful study under high magnification of a section stained with Mallory's connective tissue stain shows the following condition. The whole appears to be made up of numerous branching and redundant processes lined with epithelial cells which seem to have toppled over upon each other and to have been crushed together. Where the masses are of looser consistence many minute spaces may be seen which intercommunicate and are bounded by these outgrowths of epithelial cells carried upon a fine supporting stroma. Peripherally this structure is attached to the swollen and hyaline basement membrane of the capsule, but centrally it rarely reaches or adheres to the glomerulus. There is, practically always, at least a potential capsular space internal to the "crescents" and broken across only by adhesions which are quite different in structure from the latter.

Such masses of proliferating cells as a rule appear crescentic only when cut in a plane parallel with the stem of the tuft and if the section is at right angles to the latter, the glomerulus lies in the center completely surrounded by masses of capsular epithelium. The proliferation usually stops rather abruptly at the entrance of the tubule, but now and then strands of cells project into it for a short distance. Many desquamating epithelial cells apparently derived from the Malpighian body are found in the tubules near their parent glomeruli.

In many tufts masses of fibrous tissue extend from capsule to glomerulus and these may cover as much as a third of the circumference of the latter, or on the other hand consist of thin and threadlike bands. In this manner the capsular space may be split up into several smaller cavities which are intercommunicating and eventually open into the space leading to the tubule. These are all lined with epithelium and contain only an occasional desquamated cell. Peripherally the adhesions appear to be directly continuous with the pericapsular connective tissue through gaps in the membrana propria, but centrally they seem merely attached to the intercellular substance rather than in direct continuation with it.

The pericapsular connective tissue as well as the membrana propria is swollen and stains quite intensely blue with Mallory's connective tissue stain. An actual increase in the amount of connective tissue does not appear in the sections cut through the center of the glomerulus. A deceptive appearance is obtained in those sections passing through the pericapsular tissue only, which may cause one to suppose a great increase in connective tissue, but examination in serial section corrects this view. A slight increase is found at the point of origin of the adhesions and once or twice a small blood vessel is seen to pass into the glomerulus at such a place. The membrana propria is interrupted at several points where there are no adhesions but as yet invasion of connective tissue through such gaps cannot be seen.

Many of the tubules are filled with homogeneous or faintly cellular hyaline casts and some of them are dilated. Occasionally red blood cells are seen in them and also desquamated glomerular or tubular epithelium. The lining cells are swollen, especially those of the convoluted portion and many of them contain fat and a few large hyaline droplets. The interstitial tissue is quite œdematous and in places infiltrated with small round mononuclears and plasma cells but there are only a few polymorphonuclears present. The connective tissue seems more prominent than normal, perhaps because the fibers are separated by the increase in interstitial fluid.

Discussion.

Before discussing the significance of this case and attempting to correlate the findings with the observations and opinions of others, it is necessary to decide quite definitely its position among the various forms of glomerular lesions. Among those forms of nephritis in which the glomerular changes are prominent there are two types which must be sharply distinguished from the one described above.

The work of Lenhartz,[36] Löhlein,[1] Gaskell,[37] and Baehr[14] has defined quite clearly a form of glomerulo-nephritis associated in many instances with subacute or chronic endocarditis and in which the Streptococcus viridans (Schottmüller) seems to be most frequently the etiological factor. To quote Baehr:[4] "The salient features of the pathological picture are first, the involvement of one or more loops of a variable number of glomeruli;

secondly, the absence of any visible disease in the uninvolved glomeruli, and in the uninvolved portions of affected glomeruli; thirdly, the association in most of the bacterial cases of all the various stages of the glomerular process often seen in a single microscopical section." The inability to distinguish this type from the true toxic glomerulo-nephritis in which typical crescent formation is found has led to great confusion and erroneous conclusions. A toxic influence affecting the entire Malpighian body is quite a different process from the lodgment of emboli of bacteria in certain loops of some glomeruli, although as Ophuls[23] has stated the fundamental lesion in both types may be chronic sepsis. At least one instance of such confusion may be cited, namely that of the report of Herringham and Thursfield[24] dealing with the formation of "crescents" in which a plate shows typical changes of this embolic type. It is also possible that the thrombi as frequently described in the glomerular vessels have been of this derivation.

Quite a different lesion is that of the second type which must be differentiated from the one described here. It is dependent upon changes in the arterioles of the kidney, frequently accompanied by similar lesions of the small vessels of the brain, spleen or elsewhere. Such changes in the kidney were originally described by Gull and Sutton,[28] and have been more recently investigated by Jores.[29] There should be no confusion with this form in which the picture is merely one of hyaline change and fibrosis of the glomeruli with no epithelial proliferation. It is obvious that deductions drawn from a glomerulo-nephritis of this type cannot be applied in general to all glomerular lesions or specifically to such as the one reported above with any hope of arriving at correct conclusions.

Furthermore, within this one type confusion may arise from the failure to differentiate between various stages of the lesion. Thus, in the early glomerulo-nephritis one finds the tuft filled with cells of an endothelial type or with wandering cells from the blood, so much so that the capillaries have the appearance of being compressed, and one is tempted to consider this factor as the cause of the lesion seen later. Again, a careful study of the capillaries in the more acute stages shows, as has been emphasized by Langhans,[7] the presence of thrombi of cells and of fibrinous and hyaline material in the capillaries of the tuft, which also would seem capable of bringing about serious changes. It must not, however, be forgotten that these are the accompaniments of an acute inflammation and probably do not play a prominent part in the later stages.

This kidney is classed as belonging to the subacute stage of a toxic glomerulo-nephritis which according to Löhlein[1] ultimately terminates, if death or resolution do not occur, in a nephrocirrhosis secundaria (Aschoff[40]). Crescent formation is characteristic only of this form of nephritis (Gaskell[37]).

Inasmuch as the picture here is not obscured by acute inflammation or excessive repair it should be possible to determine which factors in the development of the lesion are essential and permanent and which are incidental and temporary.

Is then the obliteration of the blood vessels as described by so many authors a permanent and causative factor? As noted in the description, every glomerulus contains some capillaries which are filled with blood and the number of such vessels is as great or greater than that seen in the glomeruli of several normal kidneys examined. In fact this appearance is normally so variable, that the lack of blood in a tuft is of questionable importance. Its presence, on the other hand, is positive proof of the patency of the vessels in question. The arteries at the base on examination in serial section can be followed into the tuft to the point where they break up into smaller branches and in most instances are wide open and filled with red blood corpuscles. This is true even where the hyaline degeneration and epithelial proliferation is most pronounced. Reichel,[2] Fichera and Scaffidi[26] have called attention to the same normal appearance of the blood vessels in this condition. The latter states: "in den weiter vorgeschrittenen Fällen in denen der Kapselraum fast ganz oder vollständig gefüllt, eine wirkliche kompression der Gefässchlingen nicht zu sehen war; in Gegenteil zeigten letztere auf einen Querschnitt deutliche durchgängige, mit roten und weissen Blutkörperchen gefüllte Lumina, wie gewöhnlich mit freien Lücken zwischen den einzelnen Blutkörperchen." It does not seem probable then, that the glomeruli of this type of nephritis suffer from an insufficient blood supply or that the lesion is due to such a deficiency. If they have so suffered in the past, it is hard to understand how lesions so severe as the ones noted by many writers could take place with no permanent injury to the circulation, and yet bring about so profound a change as is seen in the glomeruli of this case.

Furthermore, no increase in the number of the cells within the tuft is found here. Either it was never present, or as seems much more probable considering the uniformity of opinion of various writers on this point, the occurrence and influence was but temporary. Thrombotic masses within the vessels were also looked for with special care, but not found. That they are a quite constant accompaniment of the earlier stages of glomerulo-nephritis can not be doubted from the frequency with which they have been observed. Löhlein[2] suggests that in the course of time these are absorbed or in some other way disposed of, which would seem to be the case here. It must be concluded that these likewise are but a temporary, and not an essential factor in the production of the later lesions of this form of glomerulitis.

The presence of connective tissue within the tuft is not proven in this case. The material staining a deep blue with Mallory's connective tissue stain is not fibrillar but quite homogenious, has apparently no connection with the pericapsular connective tissue at the base of the tuft and appears as a greatly thickened and swollen membrana propria of the capillary loops. Although such a basement membrane is not readily seen in connection with the capillaries of the glomeruli, it is possible that the hyaline changes serve to make it more easily distinguishable. Many masses of connective tissue which at first glance were taken to be glomeruli having undergone a fibrosis, are found, on examination in serial section, to be merely masses of pericapsular tissue at one pole of the Malpighian body. It is probable that these hyaline glomeruli are organized and converted into connective tissue as seen in the very late stages of contracted kidney, but such changes do not show in this case. The small amount present makes it improbable that the overgrowth or invasion of such tissue with consequent contraction can have any primary effect in the production of the picture seen here.

The last source of the possible obliteration of the blood vessels is from the abnormal growth of the epithelial cells. In the great majority of the glomeruli studied, there is a definite space between the proliferating capsular cells and the tuft as well as numerous spaces in the mass of epithelium. Such an appearance combined with compression of the glomerulus can only be imagined on the supposition that the tubules leading from the Malpighian bodies are obstructed. Although in several instances strands of epithelial cells were found lying at the point of origin of the tubule, in no case was this condition sufficiently great to block the egress of the fluid. Since the glomeruli always show some blood, it cannot be supposed that the tuft is compressed in all directions as would be the case according to this hypothesis.

This same argument will apply with equal force to the supposition that pericapsular connective tissue may compress the glomeruli by overgrowth and contraction. Constriction of the vessel at the base of the tuft by such growth was in no instance observed, although the vessel could, in most glomeruli be followed to the point of its branching into the tuft vessels. The assumption of Böhm[17] that an increase of connective tissue and a resultant contraction causes such a compression because of its greater condensation at the junction of the glomerulus with the capsule is not found to be true. He pictures the fibers as running over the capsule downward to the base of the tuft where consequently they seem relatively increased. The shortening of fibers running in this direction would not tend to constrict but rather to distend the neck of the glomerulus and consequently the enclosed vessels. To have the effect proposed they should be arranged in an annular manner about the neck and such an arrangement we have not seen.

Thus it seems that the essential changes are hyaline degeneration of the connective tissue and membranæ propriæ, and epithelial proliferation, rather than interference with the blood supply of the glomerulus and increase in connective tissue.

There are two common causes assigned for the production of hyaline degeneration*—the lack of proper nutrition, and the action of some toxic influence. It is of course possible that here the blocking of the vessels, as previously described, in the more acute stages is sufficient to produce this change. But we know that this condition is not maintained and one would expect on removal of the causal factor a rather prompt restoration to the normal. It is more reasonable to agree with Löhlein[1] that this is the result of a long continued toxic action and of somewhat the same nature as that which leads to a production of amyloid.

Herxheimer,[3] in a study of hyaline change in the glomerulus and capsule, has found it to start in the inner layer of the membrana propria and in this case the same structure shows the most profound change. Such an alteration cannot but have an important effect upon the epithelium which rests upon it. Whether this actually results in the proliferation which is seen in these cases or whether, as Herxheimer thinks, the reverse is true, cannot be definitely answered until the lesion can be produced experimentally and every gradation of it carefully watched and timed.

Within the capsular space two quite different and distinct phenomena are observed. The most constant and pronounced is the proliferation of the epithelium lining the capsule. Careful study in serial section convinces one that these crescentic masses consist of cells lying upon a supporting stroma which projects in folds and tongue-like processes, exceedingly redundant, into the capsular space. Here they are pressed to one side by the glomerulus as it expands and contracts under the varying blood pressure until they ultimately become packed in a stratified mass about the tuft.

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*By the term hyaline degeneration is meant a swelling and homogeneous appearance of the connective tissue and the membrana propria, and the tendency to take the blue in Mallory's stain with intensity. No definite micro-chemical reaction is implied by the use of this name. Indeed, it seems probable as Ophuls[2] has pointed out, that it is impossible to distinguish this from the beginning of amyloid infiltration, or, on the other hand, from the changes which are not sufficiently marked to be called hyaline.

That these proliferating cells are of epithelial origin can not be doubted. Their shape, size and arrangement upon the supporting stroma confirm this idea and there is no occasion to invoke the aid of metaplasia to explain their presence.

One cannot hold the idea of Herringham and Thursfield[24] as well as of others that these are but desquamated cells caught in a solidified exudate and pressed to one side by the expanding glomerulus. These cells attached to a definite stroma and showing no signs of degeneration are alive, and as far as can be judged from the microscopical examination, are in quite a normal condition.

It is true that mitoses are not found, but this is of slight negative importance. Gaskell,[37] Arnold and Baumgarten,[41] Crooke,[42] Löhlein[1] and others have noted their occurrence in similar cases as well as the presence of cells with two or more nuclei. Fichera and Scaffidi,[26] because of their inability to find mitotic figures and because of the occurrence of such multinucleated cells, conclude that cell reproduction takes place amitotically as has been noted in the cornea (Ranvier) and in the skin (Marchand). Such an explanation is hardly necessary, however, as those cells which contain more than one nucleus, are in our preparations, at least, degenerating and probably conform with the condition of a typical cellular division as seen by Lambert[43] in cells growing in vitro.

This process of proliferation greatly resembles and apparently is analogous to certain lesions seen elsewhere. Thus in the thyroid gland in exophthalmic goitre (MacCallum[44]), the cells lining the alveoli of the thyroid increase enormously in number and form redundant and manifold trabeculæ. Also in chronic cystic mastitis, in hypertrophy of the prostate, in coccidiosis in the rabbit's liver (Tyzzer[45]) and in many adenomata a similar appearance is found.

This epithelial proliferation must be sharply distinguished from the second change observed in the capsular space. This is the formation of adhesions as described by Goemans[18] and Engel.[25] The mode of production is very different and it is the attempt to apply deductions based on this form to the epithelial proliferation that has led to considerable confusion.

One can best conceive of the formation of these if the capsular space is thought of as being analogous to other serous cavities, as has been suggested by Engel and others. The desquamation of the lining epithelium in the acute stage leaves exposed the underlying capsular and glomerular surfaces. When these come in contact they tend to adhere, or between two such exposed points fibrous bands may be formed. These latter become organized and covered with epithelium, thus splitting the glomeruli into two or more spaces. These spaces are open and communicating with each other and also with what is left of the capsular space, thus ultimately emptying into the tubule. These cavities are in no sense cysts as has been erroneously stated. Such adhesions may be so extensive as to fill a third or more of the capsular space and render the distinction between glomerular and capsular tissue somewhat difficult to make. In some instances the organization is so complete that a small blood vessel may be seen running through such a band to the glomerulus as was first noted by Greenfield.[28]

It is in such a formation as this that Böhm,[17] Goemans[18] and Tschistowitsch[19] find reason to suppose that the capsular space is invaded by connective tissue. Such a condition as far as has been seen here only takes place in the organization of these adhesions.

The future of the proliferated cells and the manner in which the glomeruli become converted into connective tissue and hyaline masses, as seen in the secondary contracted kidney, can not be predicted from these observations. Such gaps as have been described by Böhm[17] in the membrana propria have been observed and it may well be that the crescentic masses ultimately become organized by the invasion of connective tissue through such places or converted into hyaline masses in the manner proposed by Herxheimer.[3] However, such processes follow and do not precede the epithelial proliferation.

Summary.

(1) Obstruction of the blood flow through the glomeruli is not essential to the production of the lesions in the Malphigian bodies.

(2) Cellular infiltration of the glomeruli and thrombi in the glomerular vessels are temporary and do not result in the late lesions.

(3) The characteristic and more essential changes are:

A. Hyaline degeneration of the membrana propria of the capsule and of the walls of the glomerular capillaries.

B. Proliferation of the capsular epithelium in the form of an exceedingly redundant membrane with compression of it into the characteristic "crescents."

C. The formation of adhesions between the capsule and the glomeruli, i.e., the "glomerulitis adhesiva" of Engel.

(4) The increase of connective tissue in the Malphigian bodies is slight, and consequently is not concerned in the production of the changes observed.

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ILLUSTRATIONS.

Fig. 1—The glomerular capillaries contain considerable blood and the arteries at the base can be followed into the tuft. Mallory's aniline blue: x625.

Fig. 2.—Marked hyaline change in the tuft and membrana propria of the capsule. Proliferation of the capsular cells upon a supporting stroma. Mallory's aniline blue: x625.

Fig. 3.—Proliferating cells lining the capsule and forming an exceedingly redundant membrane. Mallory's aniline blue: x1000.

Fig. 4.—An adhesion between a glomerular loop and the capsule, with formation of a redundant capsular membrane. Mallory's aniline blue: x1000.

Discussion.

DR. MACCALLUM: I have been interested in the study of this case of glomerulo-nephritis, because I, myself, have never been able to see the formation of crescents from desquamated epithelium in the capsule of the glomeruli just as is pictured in all the text books. Is that condition familiar to any of the members?

Even those kidneys which have suffered alteration in consequence of septic infection and exanthematic diseases seemed to show, too, the same condition as found in this case where the cells are by no means desquamated but rather portions of an actively proliferating tissue.

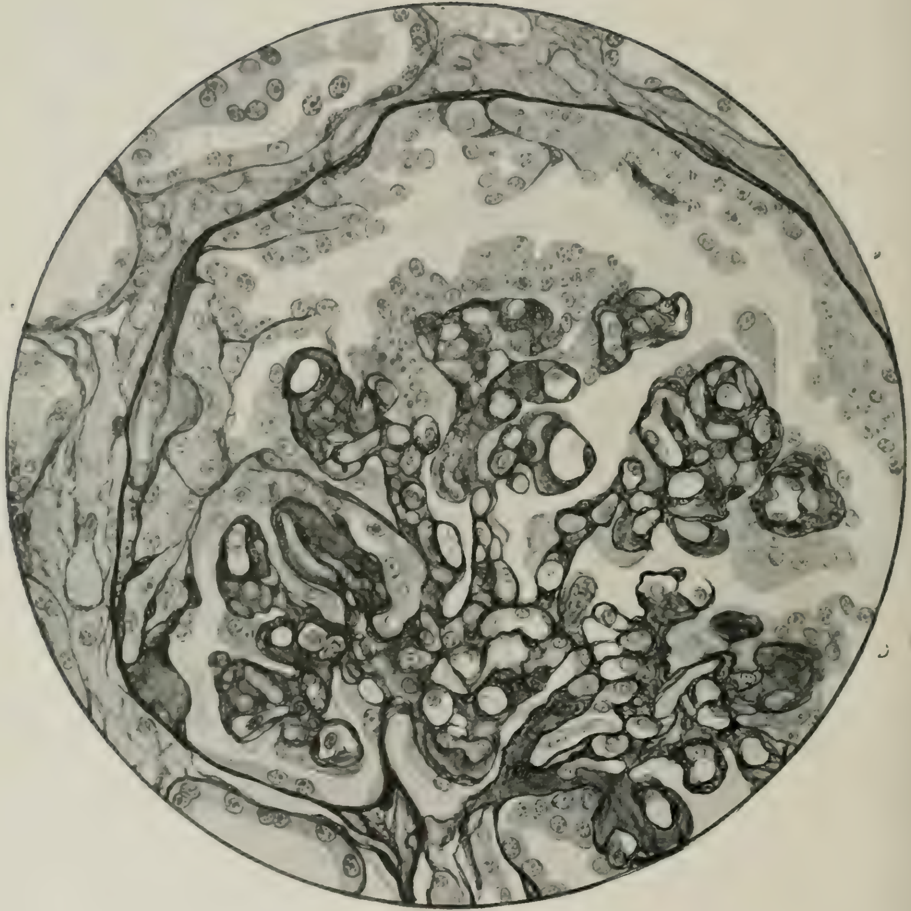

FIG. 2.

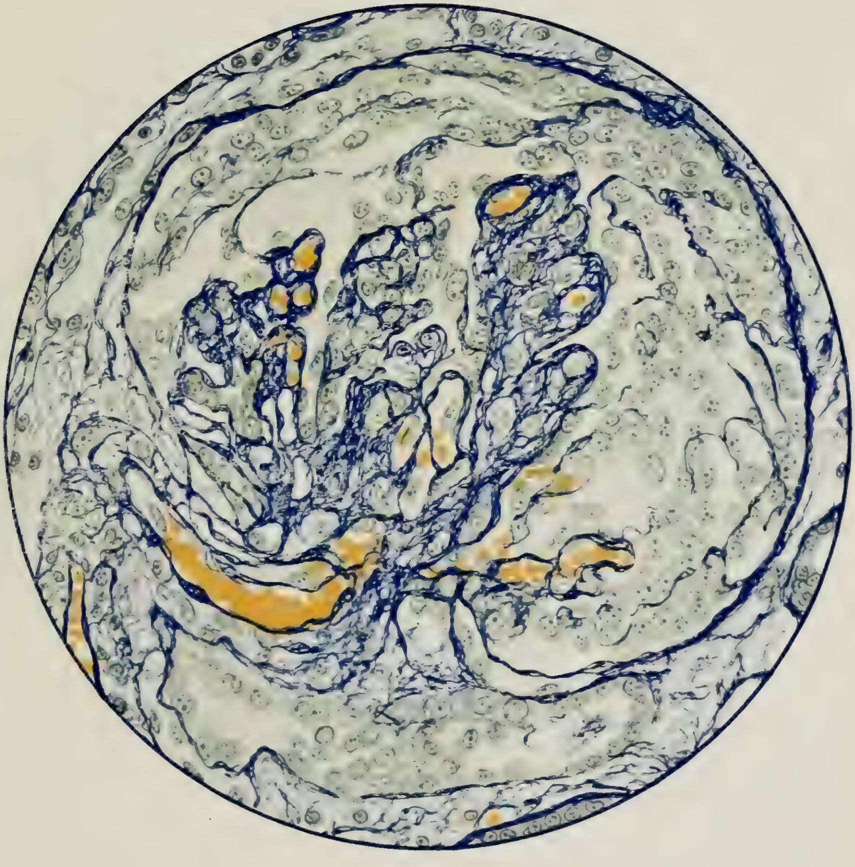

Fig. 1.

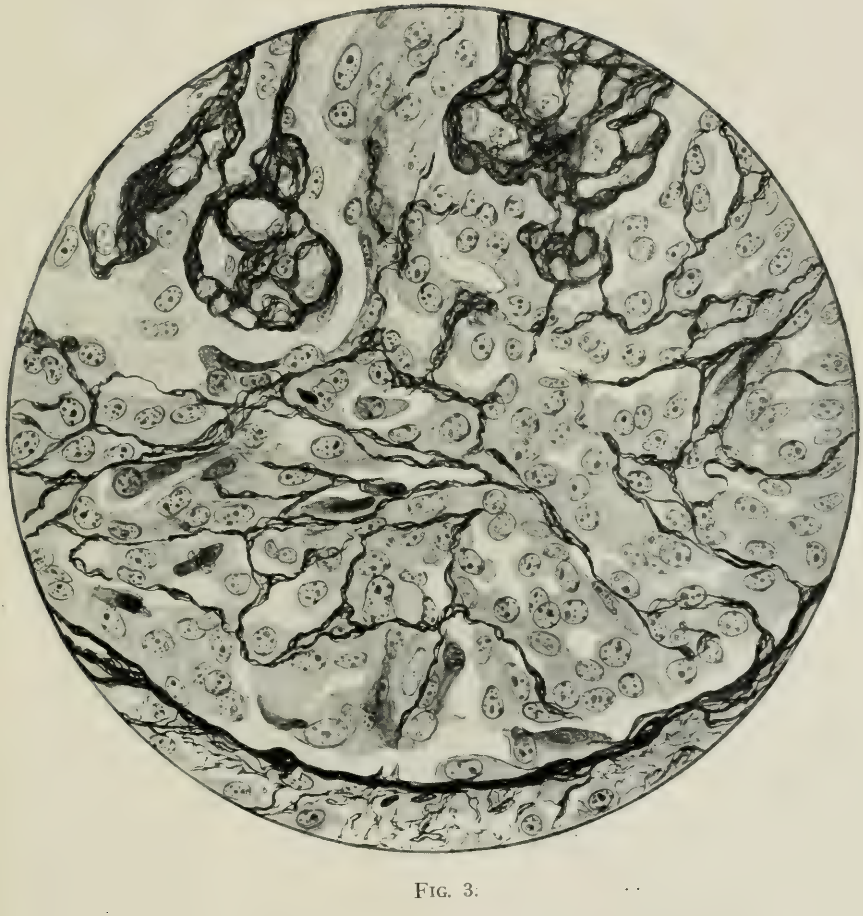

FIG. 3.

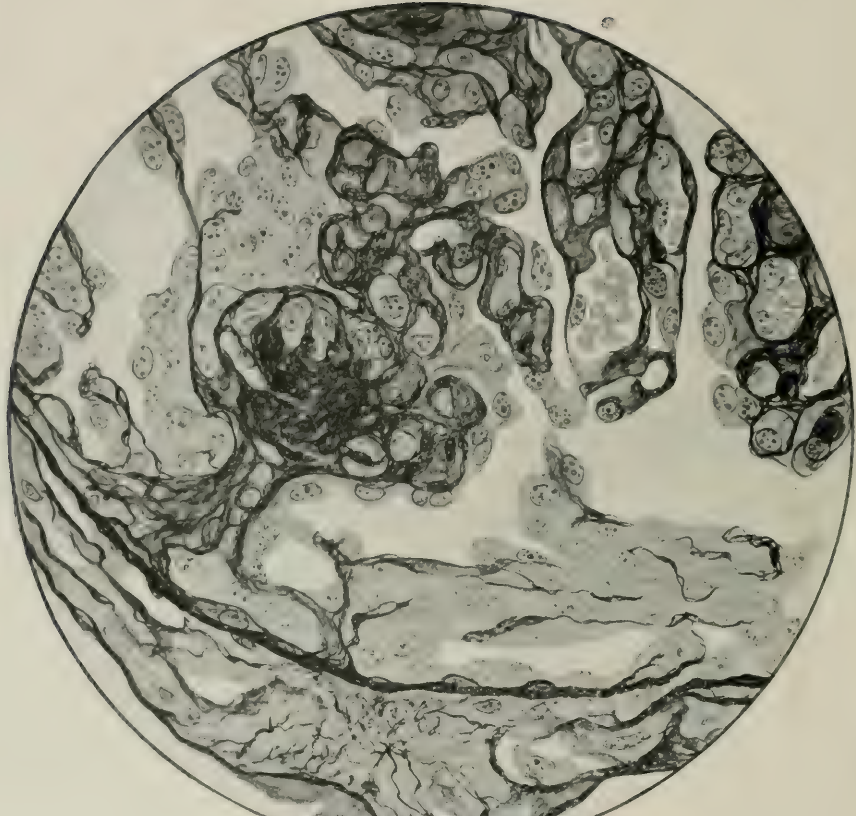

FIG. 4.

THE STRUCTURE OF THE SPLEEN AND ITS RELATION TO PATHOLOGIC PROCESSES.

Dr. Morris' report based on the work of Maximow, Weidenreich, Mollier and others and upon his own study of the spleen in various forms of acute splenic tumor tended toward the acceptance of their views that the essential cells of the splenic pulp are of the same character as the endothelial cells lining the sinuses, and that from these there may be developed independently all of the numerous types found in the bone marrow and thus ultimately those cells which circulate in the blood. This myeloid transformation of the spleen is exaggerated in infections and intoxications with the production of the acute splenic tumor, but is recognizable also in the normal spleen.

In the more severe infections, polymorphonuclears appear in great numbers, while in milder forms other types such as the myeloblast and myelocyte are predominant. The interruption of the original cell connections in the production of these new cells adds greatly to the softening of the spleen.

A detailed account of this work will be published later and elsewhere.

Discussion.

Dr. Stewart: Might not the accumulation of myelocytic cells be explained otherwise? We know, for instance, that in certain infectious conditions myelocytes are stimulated and may be found in other organs of the body.

It is possible, then, that we are dealing merely with a transportation of those cells in the spleen and not with a new formation.

Dr. Ortel: What, from your own observation, is the process of transformation of the nucleated red blood cells into the non nucleated type?

Dr. Morris: The nuclei become pycnotic and fragmented and the nuclear fragments are extruded into the surrounding blood plasma.

Dr. MacCallum: I think that there is danger in claiming the origin of one cell from another merely because they lie side by side and intermediate forms can be seen. For this reason Dr. Stewart's objection must be carefully considered.

At the meeting of the German Pathological Society in Strasburg, a kidney was shown in which a large area in the tissue about the pelvis was proved to be composed of bone and marrow elements and the development of bone marrow in other regions quite apart from the skeleton has long been recognized. Nevertheless the appearance of bone marrow cells scattered through the spleen may possibly have another explanation than that they are produced directly by the spleen. That it is different in different processes may be seen by the comparison of acute splenic tumor in pneumonia with that in typhoid.

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DR. W. G. MACCALLUM, *President.*

CASE OF MULTIPLE MYELOMA.

DRS. CHARLES NORRIS AND B. MORGAN VANCE. .

Dr. Norris presented briefly a case of multiple myeloma. The organs came from a man 54 years of age, a window dresser by occupation, who entered the service of Dr. Draper at Bellevue Hospital on January 26th, and died October 20th of the present year. Seven months before admission he complained of stiffness and tenderness in the neck and ribs; the pain increased rapidly so that in the next two months he was forced to go to bed. The pain was worse on movement. A week before his death he developed pneumonia from which he died.

The body was poorly nourished, 176 cm. in height. The arms and legs show extreme emaciation; skin is pale and of fine texture. The lungs are everywhere congested and slightly oedematous; the upper right lobe is in a condition of red hepatization. The kidneys are large and congested. Spleen is somewhat small and fibrous. The other viscera show but little change from the normal. The sternum is thickened, soft and everywhere infiltrated with white and red tumor tissue. The ribs show numerous large and small, mostly fusiform, swellings, the largest about 3 inches in length. The tumor infiltration in the ribs is very extensive. The clavicles are also infiltrated in places with tumor tissue. The cervical vertebrae are soft, are easily penetrated with the point of a knife, and there is a considerable amount of tumor tissue which has grown through the periostium of the vertebra forming a flat mass of yellowish white tissue in front of the upper cervical vertebrae. The basilar portion of the occipital bone is softened and can be readily cut away with a knife. The lower end of the right femur shows a focus which is dark red in color; otherwise the bone marrow is normal. The upper half of the left femur is extensively infiltrated with tumor tissue with large hæmorrhagic-like areas. A few of the dorsal vertebræ examined show small tumor areas.

The microscopic examination of the viscera shows but slight changes besides those mentioned above. There are, however, recent areas of focal necrosis of small size in the spleen and the muscle of the anterior abdominal wall shows a well marked hyaline degeneration. Examination of the sections taken from various portions of the bone infiltrated with tumor growth shows that the tumor is made up of two kinds of cells—a large cell with protoplasm in which no granulations can be made out, with a large nucleus occasionally eccentrically placed with a definite nuclear membrane and with scanty chromatin network. The other cell is smaller in size with a dense, small, deeply staining nucleus and with a markedly eosinophilic protoplasm. The tumor cells are free and there is only a very scanty amount of reticulum. Dr. Norris came to the conclusion that these latter cells were erythroblasts and that the two types of cells were derived from cells analogous to the primitive blood cells of Maximow. Smears made directly from the fresh tumor and stained show no granulations. Examination of the tumor cells in the hanging drop likewise show no granulations. During life the urine contained very large amounts of Bence Jones protein. A full description of the clinical history and the microscopic findings and conclusions will be published elsewhere.

Discussion.

Dr. Ewing: I think that the classification of the tumors according to cell form meets with difficulty, since the cell forms seem very different in various tumors. I have seen one tumor of a plasma cell type in which the plasma cell characters were very distinct. In most of the tumors, however, the cells resemble neoplastic marrow cells of various types, as in Dr. Norris' present case.

The early authors were too narrow in their conception of tumors primary in the bone marrow. Many of the typical cases show Bence-Jones protein in the urine. Cases of metastases have later been added to the group and the tendency has been steadily to enlarge the scope of tumors originating from bone marrow cells. These cases present every degree of malignancy, and a wide scope for this disease must be recognized, since there is such a wide divergence of the cells from which the tumor can arise. Dr. Norris' case seems to have originated from the mother cells of the leucocytic series.

I have recently had opportunity to study the literature and have reached the same conclusion as Dr. Norris on the subject. The plasmomata illustrate the difficulty in distinguishing between the neoplastic and inflammatory nature of these growths.

Dr. MacCallum: I once described a case of myeloma in which the cell presented a different appearance from those in the case which Dr. Norris has just shown. The nuclei in his case are much smaller, the nucleated red blood corpuscles are more numerous and the cells are more typical of the plasma type than were those in mine.

Dr. Ewing: Was there any particular distribution of the nucleated red blood cells and did they show neoplastic characters? Is it not possible that they may have been merely normal marrow cells which had become included in the tumor?

Dr. Norris: The drawing shown comes from the prevertebral tissue in the neck which is distinctly tumor tissue and not bone marrow tissue. There are very few red blood cells, especially in the specimen from which the drawing was made.

Dr. MacCallum: A specimen which was given me by Dr. Norris from the case was stained by Miss Kirkbride to demonstrate cell granules, but none were shown. The cells also gave no oxidase reaction.

ANOMALY OF THE INFERIOR VENA CAVA WITH THROMBOSIS.

W. G. MACCALLUM, M.D.

D. F., a man aged 28, who had previously been in good health, entered the Presbyterian Hospital in the service of Prof. Janeway on September 20, 1912, complaining of pain in the anterior and inner sides of his left thigh, with a lump in the groin. This was treated by massage. During his stay in the hospital his temperature was moderately high. There was a leucocytosis with increased precentage of polymorphonuclear leucocytes. Widal test negative as were blood cultures. There were clinical evidences of thrombotic obstruction of the veins of the lower extremities and pelvis. There was some oedema of legs and feet. Toward the end of his life, there were the physical signs of a lobular pneumonia.

At the autopsy (Autopsy No. 8202) performed by Dr. MacCallum, there was found the following condition. The legs were not noticeably oedematous but firm cords could be felt in the position of the great veins in the thigh. The peritoneal cavity contained no excess of fluid and the organs were normally disposed except in that the common iliac veins with all their pelvic and femoral branches were distended into firm masses and surrounded by dense adhesions. The inferior vena cava was only slightly embedded in such adhesions but was similarly distended and firm up to a point near the level of the renal veins. On being opened from above it was found to be filled by a brownish red thrombus which ended rather abruptly about 2 cm. below the renal veins. Below this point it completely occluded the vena cava and a similar complete occlusion could be observed in the common, internal and external iliac veins and in practically all their branches in the pelvis. Both femorals with their saphenous branches were occluded as far as they could be traced. The thrombus, especially in the femoral and pelvic veins was somewhat softened centrally, of a dark rust red color and quite intimately bound to the vein wall.

The ascending lumbar veins were open and contained fluid blood. They were extremely wide and the left had worn a wide channel in the bone along the side of the vertebral column. A probe passed through them entered the enlarged right azygos vein. Just below the openings of the renal veins there was, in the posterior wall of the vena cava, an orifice about 1 cm. in diameter through which the cavity of the vena cava communicated with that of the enormously enlarged right azygos vein. This canal, which was very thin walled, could be readily traced to its opening into the superior vena cava and through most of its course was found to measure about 17-20 mm. in diameter.

The renal veins appeared to be normal but above them the vena cava was relatively narrow, measuring about 15 mm. in diameter. It ran upward behind the liver to empty together with the portal vein into a common sinus, from which the branches normally forming prolongations of the portal vein only ran into the liver. The portion of the inferior vena cava extending from the liver to the right auricle appeared normal and the openings of the hepatic veins into it were normally arranged, but a probe passed downward in the direction of the post hepatic portion of the vena cava entered a rather narrow canal, which rapidly narrowed until it became a solid cord, the tip of which approached the remainder of the inferior vena cava as it opened together with the portal vein into the liver.

Evidently this complete obliteration of the inferior vena cava in its passage behind the liver was primary to the development of the extraordinary collateral venous circulation described. It must be thought that the blood of the inferior vena cava passed to the heart largely by way of the vena azygos, but there was also the possibility that it might pass with the portal blood through the capillaries of the liver. On the other hand, some of the portal blood may have sought out the rather easier passage to the heart by way of the azygos, especially since its tension is normally higher than that of the vena cava. This factor, as well as the roundabout path presented to the blood, must have caused a very considerable obstruction to the outflow from the vena cava, and this probably constituted the important predisposing factor in the development of so extensive a thrombosis of the veins of the pelvis and lower extremities described.

These conditions are made clear by the drawing Fig I.

Fig. 2 is a diagram of the development of the veins in so far as they are concerned in this case, which we have made under the direction of Dr. Huntington, whom I thank for it. It shows that the inferior cava is produced in different ways in its various segments, for while the uppermost part arises originally from part of the vitelline veins, that part which traverses the liver is like the branches of the portal and of the hepatic veins, crystallized out from the original plexus of veins or sinuses into the meshes of which the liver diverticula grow. Consequently, it is easy to see how this foreshadowed condensation of the sinuses along a certain path, into one trunk might be interrupted as at (A), while it is equally easy to understand that a connection with that group which becomes the intrahepatic portal might persist, although usually obliterated as at (B). From the liver the condensed path of the future vena cava forms connections which are normal in this case, with the subcardinal plexus, and through this with the complex and frequently changing plexus of supra- and post-cardinal veins which finally form the lower part of the cava. In this case the original wide connection of the post-cardinal vein which forms the azygos seems to remain. The vertical line of somatic anastomosing branches which come to form the ascending lumbar veins equally retain their connection with this azygos vein.

On the whole we have, as it appears, a failure in the coalescence of sinuses high up in the hepatic plexus to form the vena cava inferior at that point. Below this its formation is perfect enough but it retains some of its original sinus connections and thus empties into the portal trunk. The persistence of the azygos connection is evidently secondary and establishes the collateral circulation from the lower regions.

Discussion.

DR. EWING: Was there in this case any disturbance in the portal circulation?

DR. MACCALLUM: The clinicians noted only the thrombosis and pneumonia. There could not, therefore, have been any great disturbance in the portal circulation. The condition might have caused dilution of the blood but there was no obstruction of the portal vein. If there had been any disturbance it would have been due to the passage of the venous blood through the liver.

ILLUSTRATIONS.

FIG. 1.—Diagram of conditions found in case described.

A. Obliterated trunk of inferior vena cava.

B. Obliterated ductus venosus.

C. Obliterated umbilical vein.

D. Junction of lower part of inferior vena cava (F) with (E) portal vein. GG. Enlarged right azygos vein opening into vena cava at I just below renal veins and above the termination of the thrombus. (H).

FIG. 2.—Schematic diagram of development of body veins. Probably all processes shown here do not occur simultaneously. The cross hatching indicates the channels which normally persist.

A. Path of formation of vena cava inferior in the hepatic plexus. This is evidently the point at which obliteration took place in this case.

D. Shows the way in which connection might persist between the vena cava and the portal E. F the upper extra hepatic part of the vena cava forming connections with the subcardinal plexus.

I. The persistent connection of the postcardinal trunk with the plexus which goes to form the lower vena cava. This constitutes in Fig. 1 the connection I of the right azygos with the vena cava. J the supra cardinal plexus which finally becomes the lower trunk of the cava liberating the ureter.

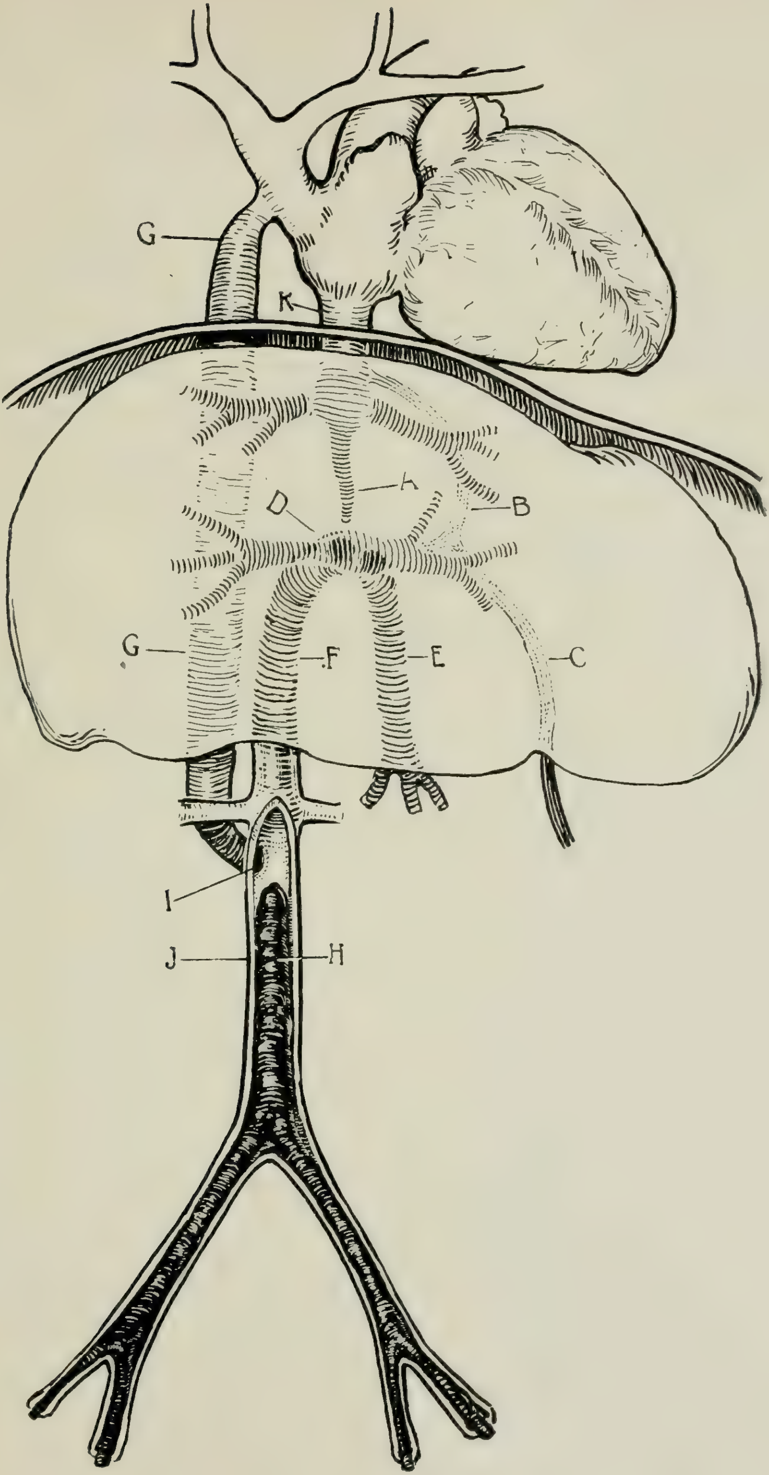

FIG. I.

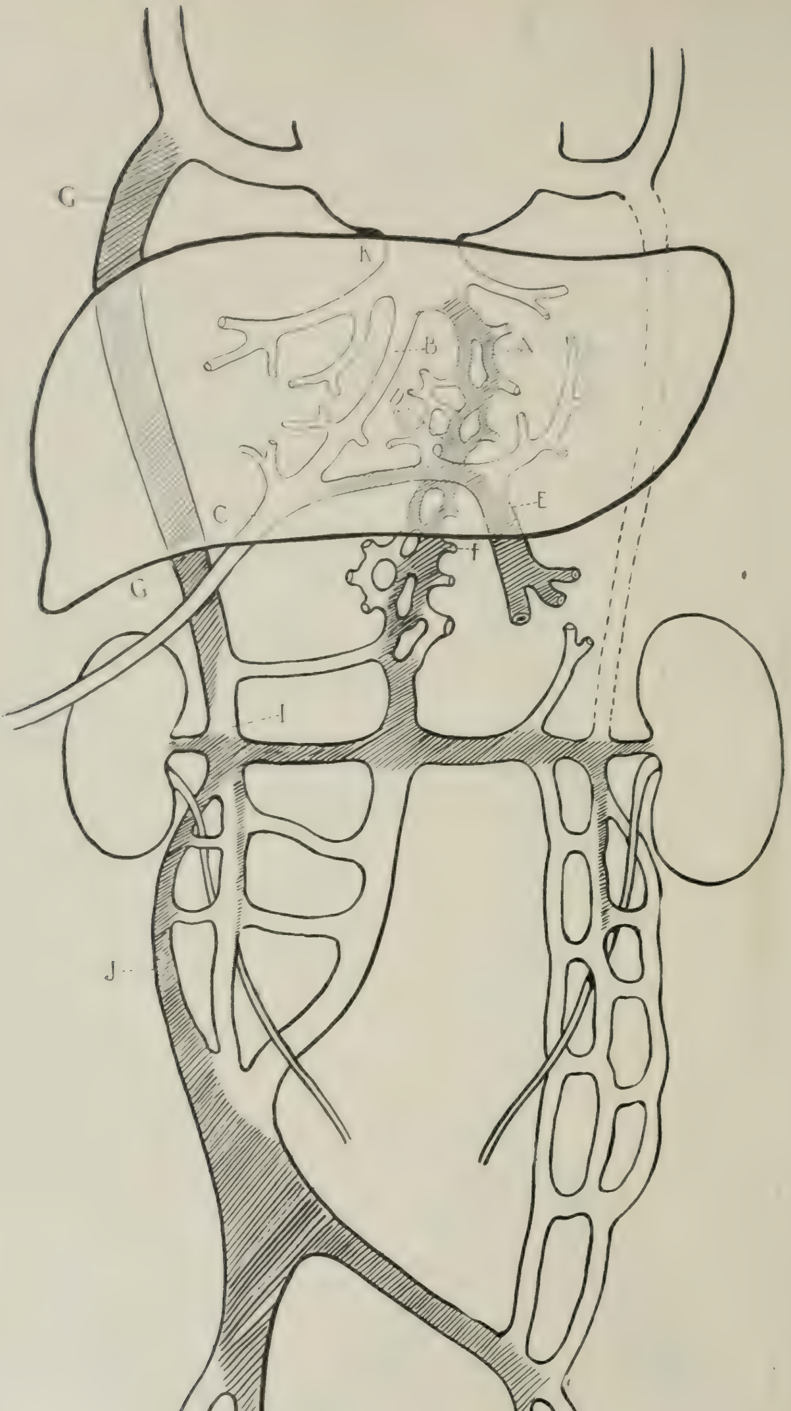

Fig. II

MUCOCELE OF THE APPENDIX.

O. V. HUFFMAN, M.D.

False diverticulum, that is hernia of the mucosa and submucosa through the muscular wall, has been described as occurring in the appendix by many authors. In addition to the simple hernial sac there occurs frequently a more complicated condition, a condition where the sac is not completed by epithelium, and mucus is held in a mesh of connective tissue. This condition was regarded as colloid cancer by Virchow and Rokitansky, but later observations have revealed its benign nature. In fact most of these tumors have been discovered quite by chance either during an intra-abdominal operation or at autopsy. These herniæ or mucoceles are generally regarded as having had their origin in a remote inflammatory process. It is because the specimen here presents several points of interest in regard to its etiology, that I am reporting it.

Case: The appendix was removed by Dr. Cragin, at Sloane Hospital. The patient had been observed previously by Dr. Levin. The patient is a woman, married, about thirty years of age. Four months ago she had an attack of pain in the right iliac region, accompanied by some fever, and four months previous to that attack she had had a similar one. Dr. Levin reports that there were marked symptoms of local peritonitis. The appendix was removed during an intra-abdominal operation for retroversion of the uterus. A moderate sized lipoma was also removed from the buttock.

Gross Description: The appendix was about 5 cm. in length. Near the distal end, it was surrounded by a mass composed of small cysts, filled with clear gelatinous contents. On opening the lumen of the appendix by a longitudinal incision, it was observed that just to one side of the lumen, before reaching the cyst, there is a dense fibrous mass, about 1 cm. in diameter. This mass causes no occlusion of the lumen. The lumen becomes lost in the cystic mass. The cystic mass is about 2x3x3 cm.; it is divided into numerous small compartments. Distal to where this cystic mass communicates with the lumen of the appendix, the appendix is found in an apparently normal condition.

Microscopical Description: Section 1; Taken from the portion of the appendix proximal to the tumor; this shows normal mucosa and muscularis.

Section 2; Taken from the portion of the appendix with the fibrous nodule, just proximal to the cystic tumor; This shows normal mucosa, and to one side a large mass composed of hyaline and cellular connective tissue beneath the muscular coat.

Sections 3 and 4; Taken from the cystic tumor. Here one finds a remnant of normal mucosa, which no longer forms a lumen but is present simply as a tape, between which and the peritoneum there is a mesh of connective tissue filled with mucus. In these transverse sections the epithelium of the normal mucosa becomes gradually reduced to a layer of very low and small cells, which can be traced no further into the cystic mass.

Section 5; Taken from that portion of the appendix distal to the tumor. Here one observes a section through a normal appendix, and a portion of the overlying, so-called hernial, protrusion of mucus membrane belonging to the cyst.

If tumors such as these are to be regarded as a result of inflammation and weakening of the walls of the appendix, thus permitting a protrusion of the mucosa, there should be some explanation in this case as to the normal condition of the distal portion of the appendix, and some explanation for the gradual transition of normal mucosa into the cystic tumor. These tumors are explained by most authors as being caused by a damming back of mucus against a weakened portion, both the obstruction and the weakening being a result of inflammation. In this way, Edel explained a similar case where, too, there was a mass of scar tissue just proximal to the deverticulum. To offset this case, however, is one reported by Fischer, where the constriction and obilteration of the mucosa were distal to the diverticulum. It is also of interest to note that in Fischer's case, where the muscularis was missing, the connective tissue instead of bulging outward, was drawn towards the lumen of the appendix. I mention this, because it suggests that it would require more than a sub-peritoneal or intra-muscular inflammation to cause a hernial protrusion; that the strong layer of connective tissue in the submucosa would have to be destroyed. An ulceration destroying the wall of the appendix and producing a tumor such as the one shown here would be unlike the result following ulceration in any other portion of the alimentary tract.

As to the possible congenital origin of these tumors, it is to be mentioned that Hedinger found an appendix with diverticula in a newly born infant, and that he sought to explain the origin of these tumors generally as of such origin, but that Winkler, who has made an extensive study of the diseases of the appendix, is not able to find any further evidence for such an explanation. Still there remains the fact that the majority of the tumors, such as the one reported here, have been found accidentally, either at autopsy or during an intra-abdominal operation for some other purpose.

To summarize then, this specimen is of interest, because of the normal condition of the appendix both above and beyond the site of the tumor, the transitional portion of the epithelium, the clinical history of appendicitis, and the inadequacy of the obstruction theory for the production of such a condition.

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Discussion.

Dr. Moschcowitz: Some time ago we had a case of mucocele of the appendix at the Beth Isreal Hospital. The appendix was removed during the course of an abdominal operation. At the tip was found a small cystic mass the size of a millet seed. On section this showed a large cavity filled up with connective tissue, which went out through a small hernia in the muscular coat; there a hematocele was formed and I gathered the impression that there had been distension of the muscular coat.

Dr. Wood: These cases of mucocele are also very interesting from an aspect entirely different from that brought out; that is, the differential diagnosis between this lesion and gelatinous carcinoma. As every one knows, there are cases of gelatinous carcinoma arising in the intestine in which the entire mass is composed of a few strands of connective tissue lying in a clear jelly-like substance, and none of the characteristic signet-ring cells can be demonstrated. Keeping this fact in mind it becomes difficult to say without thorough examination of a specimen of mucocele that no malignant growth is present. The most important differential point is the fact that in the mucocele the gelatinous substance penetrates between the muscle tissue and the connective tissue strands, leaving them unaltered; while in the gelatinous carcinomata the tissues are separated by the tumor which forms more or less roughly spherical alveoli, thus compressing and distorting the normal structures through which it grows. In the specimen of mucocele of the appendix which we had some time ago at St. Luke's, a prolonged examination of many sections was necessary before this point could be cleared up, as at first I was quite certain that the lesion was of a malignant nature.

Dr. Ewing: Dr. Huffmann has just presented a case of mucocele of the appendix. Dr. Moschcowitz has mentioned another. Dr. Wood a third. A fourth is being presented before the Surgical Society to-night, and we have a fifth at Cornell, and yet the etiological factors are but vaguely understood. Would not it be well for some one to gather together all of these cases and investigate the modes of origin of the process?

Dr. Huffmann: Many cases have been reported but there is great confusion in the literature concerning them. Some authors report them as tumors, others as retention cysts.

CONGENITAL CYSTIC MALFORMATION OF THE LUNG.

ALWIN M. PAPPENHEIMER, M.D.

The case presented illustrates a rather unusual type of congenital malformation of the lung, examples of which are found in the literature under such divergent terms as Congenital Cystic Malformation, Fetal Bronchiectasis Polycystic Degeneration of the Lung, Papillary Bronchial Adenomata, etc. The discordant nomenclature indicates the different views which have been held as to the genesis of the condition.

The case is from the service of Dr. Studdiford at the Nursery and Child's Hospital, and I am indebted to him for permission to report the clinical findings. The mother of the infant was brought to the hospital in the seventh month of her pregnancy, suffering from a severe pyelitis, with uremic symptoms. She is still severely ill, but apparently recovering. Soon after her admission, she was spontaneously delivered of a premature male child, which lived for about three hours under artificial respiration. During this time, it was only moderately cyanosed, and made some spontaneous efforts at breathing.

There were four previous children, all living, and one spontaneous miscarriage, two years ago. No direct or indirect history of syphilis could be obtained from the parents, but a Wassermann reaction taken after the child was born, proved to be strongly positive.

The autopsy was performed forty-two hours after death. The body was that of a 42 cm. obviously premature male infant. There was marked lividity of the head and shoulders. Cord still moist. Eyes, ears, nose and mouth normal. Skin shows no lesions. No external anomalies. Umbilical and hypogastric vessels contain fluid blood.

On removing the sternum, a large part of the anterior surface is seen to be occupied by the enlarged upper lobe of the right lung, which extends slightly beyond the median line, from the second rib to the liver. (Fig. 1.) The heart is displaced to the left, the apex lying beneath the fifth rib, 3½ cm. from the median line. The thymus is also pushed over to the left, extending to the third interspace. The left lung appears relatively small and collapsed, lying in the posterior part of the thorax.

The right upper lobe is extremely voluminous, 7 cm. from apex to lower border and about 6 cm. in width. The surface is smooth, showing none of the normal lobular markings; it is reddish pink in color, rather translucent and elastic. There are scattered small hemorrhagic blotches beneath the pleura.

On the septal surface, especially near the posterior portion, there are numerous rounded translucent elevations, up to 1 cm. in diameter, through which clear fluid can be seen. These are separated by more opaque whitish septa.

The apex of the lobe is occupied by a cap of normal appearing lung tissue, which overhangs slightly the rest of the lobe behind and is sharply demarcated from it.

The lower and middle lobes are relatively small, darker in color and evidently poorly aerated. The same is true of the entire left lung, which shows no external malformations.

After hardening, the specimen was injected through the trachea, under moderate pressure, with a solution of Berlin blue in gelatin. All the lobes were readily injected, although the diffusion of the mass was somewhat irregular, owing to the preliminary fixation. In the right upper lope, however, the injection is limited absolutely to the cap of normal appearing lung tissue which constitutes the upper pole. A section made through the upper lobe shows a sharp and very distinct demarcation between the upper injected portion and the lower uninjected part.

A dissection of the main bronchus shows that there is a branch of small caliber, derived from the right main primary bronchus, distributed to the cap of normal lung tissue at the apex of the lobe. But even a careful search fails to show any branch running to the lower spongy portion, into which a bristle can be passed. The bronchi to the middle and lower lobes and to the left lung, are normal. Nor is there any abnormality found in the distribution of the pulmonary arteries and veins.

A section through the upper lobe shows a sharp division into two portions—an upper injected part resembling normal lung tissue but partially atelectatic; and a larger lower portion, in which the tissue is decidedly paler and spongy in structure, being composed entirely of smaller and larger cystic spaces separated by rather stout septa or trabeculæ. These cystic spaces reach the size of almost 1 cm., the largest ones being situated near the septal surface. They are approximately circular in outline. In the depths of the tissue are several rather thick tubular structures; whether these are vascular or bronchial in nature cannot be determined from the gross appearance. No tubular structures are seen near the hilus.

Section through the remaining lobes of the right lung and through the left lung show nothing abnormal. The lung tissue is poorly aerated and hyperæmic; the injection mass has penetrated somewhat unevenly, but is present in all the lobes.

The *heart* is normal in size and conformation. There are no valvular lesions or anomalies. The foramen ovale is somewhat more widely patent than one would expect at this age, but is well formed. The ductus cannot be probed, and is almost, if not entirely closed.

Liver is normal in size. There are several sub-capsular hemorrhages on the anterior surface. The surface of the cut section is very oedematous, of a uniform greyish pink color, without lobular markings.

The *spleen, kidneys, adrenals and bladder* show no noteworthy changes. The *thyroid* is large, the lateral lobes extending to the face of the pharynx. Behind the R. lobe, there is an oval, pinkish body, 2 cm. in length, resembling thymus in texture, and proving to be such on microscopic examination. The *parathyroids* were normal, three being found.

The microscopic findings in the different organs, in so far as they have a possible bearing on the case, are as follows: The liver contains very numerous blood-forming islands. There is no increase in connective tissue. The *spleen* shows an engorgement of the sinuses; there are many nucleated red cells, but comparatively few pulp cells. The follicles are small, irregular and poorly formed. The *pancreas* shows the acini separated in places by a loose embryonic connective tissue in which are found small areas containing very numerous lymphoid cells and granular eosinophiles. These areas are especially seen in the neighborhood of the larger pancreatic ducts and arteries. A few solid nests of cells, representing poorly formed islands, are found. The *testis* contains an unusual number of capillaries, which are engorged with blood. There has been some extravasation between the tubules, and there are a few clumps of yellow pigment. The *adrenal* has a very broad cortex, in which the narrow glomerular zone exhibits the formation of distinct lumina; the capillaries of the reticular zone are congested.

Sections of thymus, adrenal, liver and kidneys examined for spirochaeta pallida by the Levaditi method, were negative.

Lungs: Sections through the spongy portion of the right upper lobe show a great number of irregular spaces, up to 1 or 2 mm. in size. The smaller ones are lined with flattened cells, are surrounded by well-filled capillaries, and are separated from each other by more or less stout septa. They resemble normal alveoli in all respects. These alveolar spaces are empty, apparently containing none of the coagulated granular material which is found in the larger cystic spaces. In the thicker septa are numerous connective tissue cells with pale oval nuclei and comparatively few collagenous fibrils. The elastic framework is well developed. In eosin-methylene blue preparations, there are found quite a number of normoblasts, some of which are extra-vascular, and a few granular eosinophiles.

The larger cysts are lined by high cuboidal or columnar epithelium, which is for the most part distinctly ciliated. The walls are not smooth, but the mucosa is thrown up into corrugated folds, which in places are extremely redundant, forming papillary projections into the lumen. Mitoses are not found, probably because of the lateness of the autopsy, since the appearances certainly suggest active proliferation.

In the lumina of the cyst-like spaces, is a shreddy or granular material, evidently not mucinous in character, and consisting in part of cast-off cilia. There are also here and there a few desquamated cells, which are for the most part round and apparently derived from the alveolar, rather than the ciliated cubical epithelium. The amount of demonstrable cyst contents is extremely small, the majority of the spaces appearing entirely empty.

From the primary cavities, tubular gland-like prolongations are given off, and may be traced in serial sections for a considerable distance. Often there is a slight constriction at the neck of the tubule, and on cross section, the small evaginations closely resemble tubular glands. Goblet cells are never found, the tubular outgrowths, like the larger spaces, being lined with ciliated epithelium. They may bifurcate before ending blindly.

The epithelium of the dilated bronchioles, for such they are, rests almost directly upon a membrane of elastic tissue, composed of three or four laminæ of stout fibers. The areolar tissue separating the cysts from one another, also contains a loose feltwork of elastic fibers. In the wall of many of the cyst-like spaces are thin bundles of smooth muscle fibers, circumferentially disposed; about most of the spaces, however, they are absent.

Some of the spaces have definitely the character of bronchi. Their wall contains small crescentic islands of cartilage, and rather stout bundles of smooth muscle fibers which, however, never completely encircle the bronchus, but are arranged in discontinuous bundles. The epithelium clothing the bronchus is of a character similar to that in the cyst-like spaces described, though somewhat higher, and in places heaped up into several layers. It is likewise definitely ciliated.

Of importance for the correct anatomical interpretation of the anomaly, is the relation of the cyst-like spaces to the bronchi, on the one hand, and to the alveoli on the other. This could be easily determined in serial sections, and it was found that the dilated spaces were not closed cysts, but in direct communication with both the larger bronchi and with the alveoli. As the bronchus passes into the dilated portion, it frequently becomes narrowed by the projection of valve-like folds of epithelium. It then widens out into the irregular cavities described, and from the terminal portions of these, corresponding to the normal infundibula, the alveolar spaces are budded off. But it is of interest to find that the transition between ciliated and flattened alveolar epithelium is not a regular and gradual one, but that different portions of the same infundibular enlargement are lined in some portions, by epithelium of the cuboidal ciliated type, in others, by flattened alveolar cells.

The blood vessels, both in the normal and the spongy lung tissue show no departure from the normal structure.

Since the case described by Meyer[1] in 1858, similar cases have been reported from time to time by Grawitz,[2] Balzer and Grandhomme,[3] Couvelaire,[4] Dionisi,[5] Arnheim,[6] Pepere,[7] Stoerk,[8] Sandoz,[9] Buchmann[10] and others. The cases fall into two groups —those occurring in premature or new-born infants, in which the condition is apparently incompatible with life; and the cases found in later life and interpreted for various reasons as congenital. These instances of fetal bronchiectasis found in the lungs of older individuals, are often obscured in their interpretation by the presence of secondary inflammatory changes, but the complete absence of pigment in the affected area is usually taken to indicate their congenital origin.

As regards the cystic malformation in the new-born, two types may be distinguished, between which all transitions have been described. The first is illustrated by a case reported by Wechsberg.[11] Here there was found a tumor in the left pleural sac attached merely by a fibro-vascular pedicle to the pleural covering of the oesophagus. It contained numerous cysts filled with clear fluid and showed microscopically the same structure as the case shown here. In this case, there was, of course, no communication with a bronchus. Wechsberg believes that the tumor arose from an accessory lung Anlage, arising separately from the oesophagus, with secondary obliteration of the connecting canal. Klebs had previously described such a rudimentary lung given off below the diaphragm.

In contrast to this case in which the cystic lung tissue is entirely separated from the normal lung, are the cases such as those of Arnheim[6] and Pepere,[7] in which the cystic changes affect an entire lung, or even both lungs to a greater or lesser degree. In the majority of cases, the cystic change has been restricted to a single lobe or to a portion of it, as in the case presented.

A communication between the dilated spaces and the larger bronchi has been established in certain cases by inflation; in many of the cases, however, there is a definite record that the cysts contain fluid and are not connected with the bronchi. Thus Couvelaire[4] has described a specimen in a new-born child in which the tissue at the hilus of the affected lobe contained not a single bronchus.

The various views regarding the genesis of the condition, bay be grouped under three headings:

I. The condition is to be looked upon as simple arrest of development at a period more or less advanced. This theory explains the embryonic structure of the bronchioles and infundibular spaces and the absence of completely differentiated bronchi, but does not give a reason for the dilatations or cyst formations. Moreover, in those cases in which there is an absence of the larger bronchi, it is necessary to assume that these have undergone a regression or secondary obliteration. We have an analogy for such a process in the normal obliteration of canals derived from the fore-gut, as in the case of the pharygo-hypophyseal duct, the thryo-glossal duct, and the canals in the cervical portion of the thymus. It does not seem strained to assume that a similar process may occur abnormally in the developing lung bud, but the actual demonstration of such a secondary obliteration has not been given.

II. The entire process is the result of a fetal inflammation, with inflammatory stenosis or atresia of the bronchi, and bronchiectatic dilation of the distal portions from stagnation of the secretions. This explanation must be discarded for those cases in which a communication with the bronchus persists. It is further objectionable in so far as no histological evidence pointing to the occurrence of an inflammatory process has been brought forward. The only exception is the case of Balzer and Grandhomme,[3] in which the unaffected lung showed definite syphilitic changes, and a thickening about the vessels and bronchioles is described in the cystic lobe. But here, as Couvelaire[4] and Humbert[12] have pointed out, there may have been simply a coincidence, the anomaly occurring in a syphilitic lung. None of the other recorded cases in young infants have shown inflammatory changes and where such are present in later life, they are doubtless secondary. Furthermore, the formation of bronchiectases by simple stagnation of secretion, is questionable, and the irregular appearance of the dilated spaces with their villous or reduplicated lining, does not in the least suggest such an origin.

Nevertheless, the occasional association of syphilis with this anomaly, as in the case of Balzer and Grandhomme,[3] in the two cases reported by Sandoz,[9] and possibly in the present case, is of interest; and it is possible that a more careful inquiry would show that in the production of this as in other anomalies depending essentially upon an inhibition of development, syphilis plays a dominant role.

III. The third hypothesis is that maintained by Stoerk,[8] which interprets the condition as a tumor growth. Stoerk has applied the term "cystic fetal bronchial adenoma" to the neoplastic process, and believes that it is possible to differentiate cases of this type from cases of fetal bronchiectasis due to inflammatory stenosis. His principle argument for considering the condition as a neoplasm is that the dilatation of the bronchi is accompanied often by tubular outgrowths into the septa. It seems to the writer that little is gained by applying the term tumor to an anomaly of this sort. That the failure of complete differentiation is accompanied by a normal or even excessive growth, is probably true, and to this excessive growth, rather than to a passive distension by secondary products, is attributed the formation of the dilated spaces and the increased size of the affected lung or lobe. Whether one shall apply to such a simple overgrowth of undifferentiated tissue the term neoplasm, is of no particular consequence, since such a view adds nothing to our knowledge of the causation of the condition.

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ILLUSTRATIONS.

Fig. 1.—Heart and Lungs: natural size. Only the malformed upper lobe of the right lung is seen from the anterior aspect.

Fig. 2.—Section through right upper lobe. Dilated bronchioles lined with ciliated epithelium; in the septa, normal alveolar tissue. x 80.

Fig. 3.—Section through dilated bronchus and adjacent tissue. B.—Bronchus; C.—Cartilage; M.—Smooth muscle fibers; Br.—Dilated bronchioles. x 80.

Discussion.

Dr. Moschcowitz asked whether in his survey of the literature, Dr. Pappenheimer had found that congenital cystic lung was associated with congenital cystic kidney. Some years ago in a study of congenital cystic liver he found that various authors frequently mentioned the association between congenital cystic degeneration of the lung, liver and kidney. Dr. Moschcowitz had come to the conclusion that congenital cystic liver was due to a malformation; and that the lesion was due to a dilatation of aberrant intra-acinar bile ducts. Fully developed intra-acinar bile ducts were found in an apparently normal liver, microscopically, in a foetus that had cystic kidneys and various congenital malformations such as supernumerary digits, encephalocele and spina bifida. In cystic livers these fully developed ducts can be demonstrated within the lobule of the liver. For these reasons, Dr. Moschocowitz has concluded that cystic liver was a result of a malformation, and, inasmuch as cystic lung was associated with cystic liver, that congenital cystic lungs were also the result of a malformation. In other words, that the spaces which made up the bulk of the lesion were primitive or embryonal bronchi which had failed in their further development.

Dr. Stewart: We are always looking for the developmental mechanical factor in the formation of bronchiectases. What is the nature of this factor in this case?

Dr. Pappenheimer, in answer to Dr. Moschcowitz, said that he had only approached the literature from the lung side. There were no cystic kidneys in his case, nor had he found any reported in the literature in connection with cystic lungs. In answer to Dr. Stewart's question, he admitted that the arrest in development did not in itself account for the dilatation, but it seemed to him that one had to assume an excessive growth in association with the arrested differentiation.

Dr. Norris: What was the character of the epithelium lining the cyst?

Dr. Pappenheimer: The spaces are lined with a columnar or cuboidal ciliated epithelium.

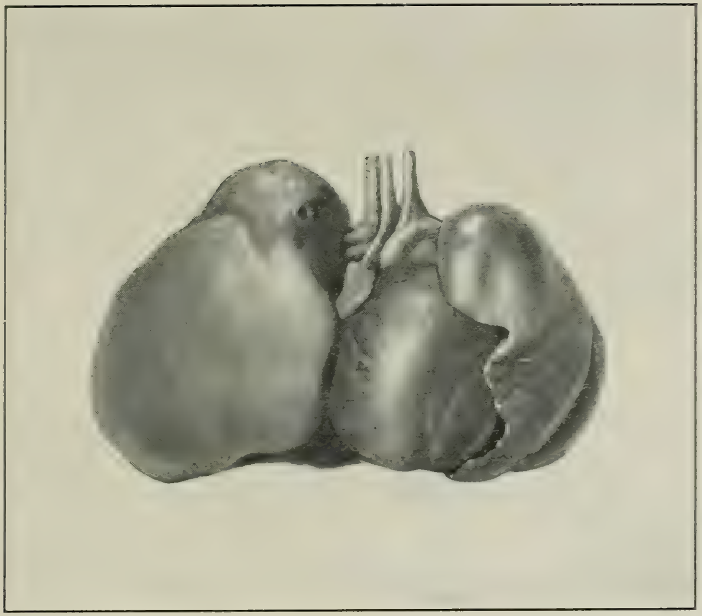

Fig. I

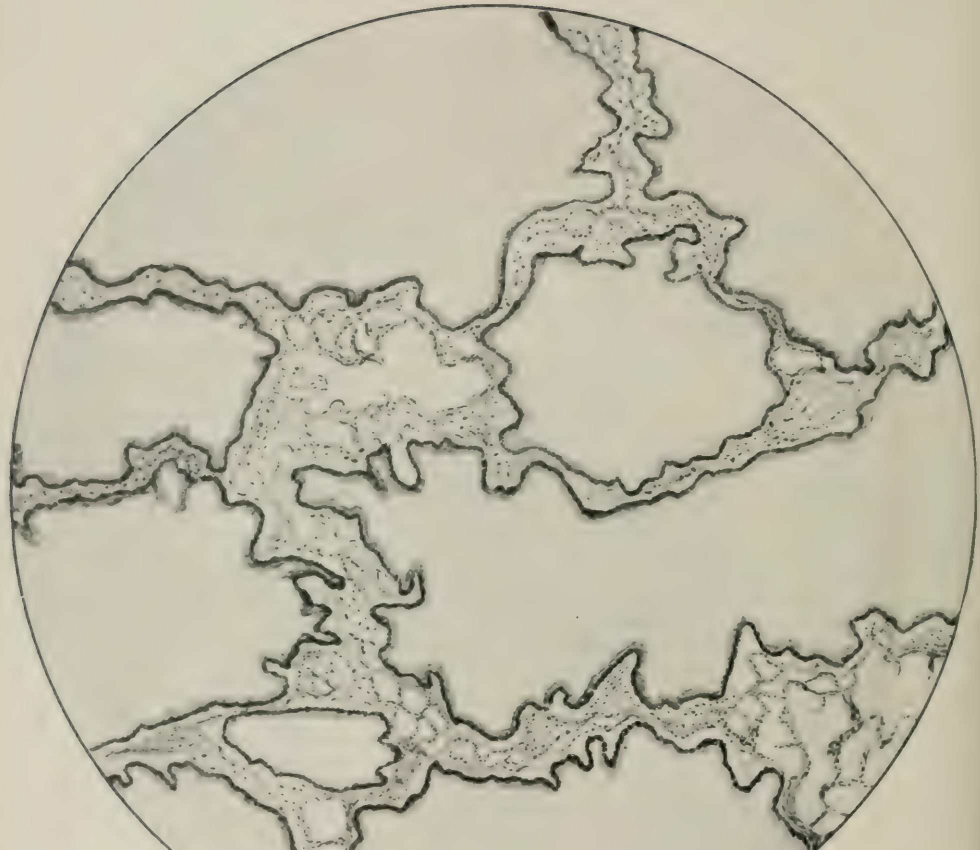

Fig. II

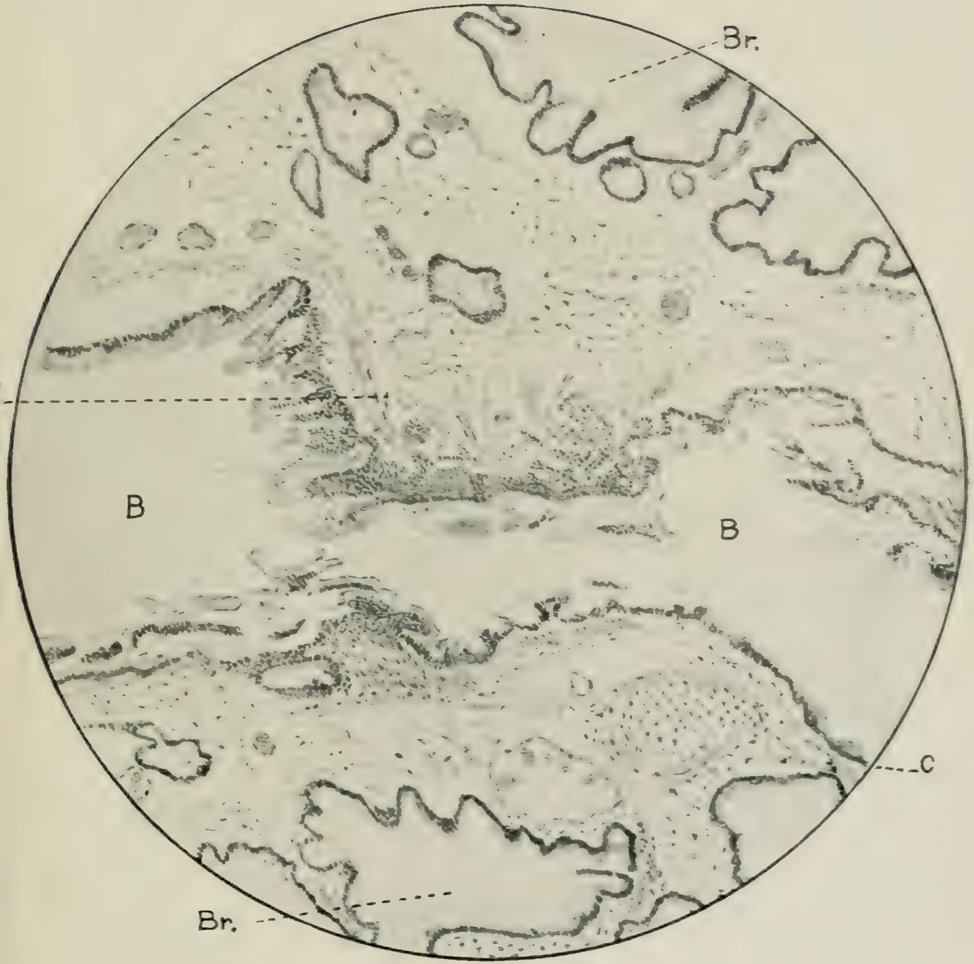

FIG. III.

THE TRANSPLANTABILITY OF MALIGNANT TUMORS TO THE EMBRYO OF A FOREIGN SPECIES.

JAMES B. MURPHY, M. D.

The phenomenon of tissue specificity, that is, the failure of transplantation of tissues of one species into the body of another, has been the subject of much speculation among experimenters, with as yet no adequate explanation. It has been of particular interest to cancer investigators, as it represents the great barrier that prevents the transfer of human tumors to lower animals. Wider experimentation has shown that this line between species is more closely drawn than was suspected, and it is even found to divide the varieties of the same species. Well-known examples of this are the failures in transplantation of the tumors of the white mouse to the brown or grey mouse, or tumors of the white rat to any other than white rats. A more recent example is that of the Rous chicken tumor,[1] which in its first transfer grew only in blood-related animals, and later only in animals of the same breed as the original fowl.

Remarkable as this phenomenon is, it has not been the subject of as extensive research as its importance would warrant. There has been a general impression that one of the immunity processes is responsible for this reaction, but no very definite evidence is at hand. Ehrlich includes an explanation of it in his ingenious hypothesis for tumor immunity, the so-called athrepsia theory.[2] This is briefly that the cells of an organism possess a certain specific binding power for the circulating food particles. When a cancer graft is introduced into an animal, if its attraction and binding power for the food particles is greater than that of the host cells, it grows at the expense of the other tissues. If, however, the binding power of the cancer is lower than that of the host tissue, the cancer cells fail to grow and die from lack of nourishment. Animals showing this latter condition are called naturally immune. The artificial immunity to inoculable cancer, produced by a previous introduction of living cells into the animals, is accounted for by the presumption that these cells bind all the available food, leaving none for the cancer to utilize in its growth. The failure of growth of a tissue introduced in a foreign species, as is naturally deduced from the foregoing explanation, comes from the inability of the cells to combine with and utilize the alien food particles. The temporary survival of cells in a foreign species host, Ehrlich claims, is adequately accounted for by the native food carried with the graft from the original species. This latter phase of the hypothesis is the one of interest in the present research.

We reported last year the successful inoculation of a fowl sarcoma into the developing chick embryo.[3] In the course of this study the interesting observation was made that the tumor grew equally well in the developing pigeon or duck embryo, whereas in the adult of these species it quickly died and was absorbed. This finding suggested two possibilities: either the embryo provides a food substance utilizable by the tissues, which is lacking in the adult, or else the embryo lacks a defensive mechanism possessed by the adult. The results I wish to report to-night were obtained with tissues from more distantly related species, namely, mammalian tissue inoculated into embryos of the common domestic fowl.[4]

The technique is very simple. A small rectangular window is cut in the shell with a sharp instrument. The shell membrane is broken and pulled back with sterile forceps, exposing the embryo and its membrane. The material used is hashed finely and injected by means of a hypodermic needle into the desired location. After the inoculation the bit of shell is replaced and sealed with paraffin. By this method I inoculated a fine hash of the Jensen rat sarcoma*[5] into the outer membrane (fused allantois and chorion) of five to seven days embryos. These were then incubated from ten to twelve days, that is, to within two days of hatching. When the shell was removed and the membrane cut and turned back, in a high percentage of instances the egg was found to have, at the point of inoculation, a rounded globular mass, suspended from the membrane by a broad, flat pedicle. The masses varied in size from 0.2 to over 2 cm. in diameter. The consistency was that of firm jelly, varying in color from pinkish grey to red. The surface was smooth and glistening, with numerous large dilated vessels coursing over it, and smaller vessels were visible in the semi-translucent substance of the tumor itself. On section the masses were found to be solid and composed throughout of this pinkish-grey, somewhat translucent tissue, with small areas of hemorrhage in some cases. The tissue was quite moist and friable.

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*This tumor was selected for the work as it is the generally known and one of the most widely worked with of the transplantable tumors.

[1] *Jour. Exper. Med.*, 1910, xii, 696.

Moreover, it was found easy to re-inoculate these embryonic grown tumors into a second series of embryos. The tumors from this second generation are of the same types as those of the first, and grow with equal rapidity. These in turn can be transferred to a third and fourth lot. This rat tissue has grown for as long as forty-six consecutive days in the foreign species embryo.

Naturally the change and possible adaptation of this tissue to the new conditions has considerable interest. As far as the morphology of the growth and of the cell is concerned, there is little or no change. The tissue when returned to the rat after the long sojourn in the foreign host gives rise to a tumor that grows as rapidly as when the tissue is transferred from another rat. On the other hand, the tissue acts differently when placed in an adult chicken. Tissue taken directly from a rat will survive for three days in the adult chicken and for about the same length of time in the newly hatched chick. On the other hand, when this same rat tissue is grown for a period in the chick embryo and then placed in the adult, no living cells can be found after twenty-four hours. This condition is also noted in the newly hatched chick. In some cases the inoculations were made a very short time after the animals emerged from the shell and they were kept in the incubator without food or water for the first twenty-four hours so as to change the conditions as little as possible. Instead of adapting the rat cell to a new host we have made it more susceptible to defensive forces.

A variety of other tissues have been grown with equal success to that of the Jensen sarcoma, namely: chick embryonic tissue, rat embryonic tissue, a sarcoma, a carcinoma, a chondroma of the mouse and the Flexner-Jobling adenocarcinoma of the rat.

Conclusions: The experiments show conclusively that mammalian tumor tissue can live and grow actively in the chick embryo, although in the adult it dies quickly and is absorbed. By transfer from embryo to embryo the mammalian tissue can be kept growing for as long as forty-six days and probably indefinitely. This proves beyond doubt the ability of the mammalian cell to utilize the food supplied by the avian embryo. There seems little doubt, from a study of the fate of the grafts of this same tissue in the young chicken and in the adult, that they possess a defensive mechanism which causes the death of the tumor cell, rather than that the grafts die from lack of nourishment. The changes that take place in the rat cells after their long dependence on the foreign species host are certainly slight. Whether a still longer period of dependence will bring about an adaptation of these which will render them capable of growth in the adult remains to be seen, but present results offer little encouragement in this direction.

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Discussion.

Dr. Lambert: In our tissue culture studies, Dr. Hanes and I found that while rat sarcoma cells may proliferate for a month or more in certain foreign plasmas (guinea-pig plasma, for example), the duration of growth in chick or pigeon plasma is, as a rule, only three to five days.

In view of Dr. Murphy's results, it would be interesting to see if there is any difference in the duration or character of the growth of rat tissues in embryonic chick plasma and in plasma obtained from chicks after hatching.

Dr. Rous: I wish, with Dr. Murphy's permission, to add an interesting feature noted in his experiments. The rat tumor grows in the chick embryo at a temperature of 41° C, whereas in the rat it grows at 37.6 C. This fact would tend to show that the regression of tumors during febrile processes, cannot be due directly to the increased body heat, as is so frequently assumed.

Dr. Levin: When a tumor is placed in the egg is it always brought in direct contact with the embryo or its membranes, or does it frequently float freely in the yolk of the egg? It is possible that in either instance the tumor cells obtain their nourishment from the yolk, and then the inocluations of the tumor into the egg are comparable to the experiments of Dr. Lambert, where rat tissue grew in vitro in chick plasma. When the yolk disappears and the only nourishment obtainable by the tumor cells is the specialised food of the chick embryo, then the growth of the rat tumor ceases.

Dr. MacCallum: Do not these tumors acquire a vascular supply?

Dr. Ewing: What is the morphology of the cells of these tumors and do they differ from those of ordinary rat tumors?

Dr. Murphy: There is no variation in the morphology of the cells; even after forty-six days' growth in the chick embryo the cells are distinctly those of a rat tumor. The structure is not so compact. In answer to Dr. Levin I would say that the tumor grows only when brought in direct contact with the chick embryo or the embryonic membranes. It receives a tremendous vascular supply, and a certain amount of stroma from the host.

A CASE OF ACUTE MILIARY TUBERCULOSIS.

A. B. EISENBREY, M.D.

Clinical History: The patient, aged sixteen months, was admitted to St. Luke's Hospital in July, 1912. The symptoms at that time were pain in the abdomen, diarrhœa, and jaundice. No family history of tuberculosis was obtainable. The patient was running a moderate regular fever. No bile was found in the urine. A diagnosis of tuberculous peritonitis was made, but at operation the peritoneum was found not to be involved, though the retroperitoneal glands were markedly enlarged. None of these were removed, however. After one month the patient left the hospital, his general condition being somewhat improved; but on November 4, he was re-admitted in a moribund condition.

Autopsy findings; There was a generalized miliary tuberculosis, notable because of the enormous numbers of tubercle bacilli found in sections of the liver, spleen, kidneys, and lungs. The peritoneum was thickly studded with tubercles, and in the ileum there were seventeen large ulcers easily recognizable from the peritoneal side, in several places causing adhesions between adjacent loops of intestine; but no perforation had occurred. The entire group of retroperitoneal glands was matted together in a mass about 12 cm. in diameter. The glands were greatly enlarged and caseated. In addition to the miliary involvement the left lung showed an ulcerative process and cavity formation at the apex. The cavity contained fresh blood clots and there was erosion of the vessels passing across it. Since the lungs were not found to be involved during the patient's stay in the hospital in July, it is reasonable to believe that the tuberculosis was primary in the peritoneal glands, that the lung development occurred later, and that the cavity in the lung acted as the distributing point for the miliary involvement.

The liver was markedly enlarged and appeared fatty. The gall-bladder was distended and its wall thickened. Firm pressure failed to force bile through the duct and it was found that two enlarged glands compressed the duct between them. On dissecting away one of the glands the bile was readily expressed. The patient was markedly jaundiced, but microscopical examination failed to show a dilatation of the bile capillaries in the liver.

Discussion.

Dr. Wood: This case is of considerable interest as showing the very short time in which a diffuse growth of miliary tubercles can take place throughout the body. The fact that no tubercles were seen at the time of the laparatomy some months before the child's death is sufficient proof that there was no generalized miliary tuberculosis at that time, so that the whole process must have been quite a recent one. Despite the lack of dilatation of the small bile ducts I still think that the jaundice was probably an obstructive one. A very moderate degree of pressure on the common duct, such as was caused by the tuberculous lymph node demonstrated, will give rise to moderate jaundice without complete obstruction of the flow and without great dilatation of the capillaries, especially if the obstruction has existed for only a short time. The sections of the liver are very interesting. I have never seen so many tubercle bacilli in one section. It looks like a sputum concentrate after the use of antiformin, the entire field being covered with organisms.

Dr. Norris called attention to the translucent foci resembling miliary tubercles, on the edges of the tricuspid valves, which Dr. Eisenbrey had shown to him before the demonstration.

Dr. MacCallum: Was the actual portal of entry determined?

Dr. Eisenbrey: The portal of entry was the cavity in the lung.

CALCIFIC AND OSTEOGENIC CHANGE OF THE LEFT AURICLE IN A CASE OF AURICULAR FIBRILLATION.

B. S. OPPENHEIMER, M.D.

The following case is reported on account of the increasing interest shown of late by general pathologists and pathological chemists in calcification and ossification and because of the rarity of these two processes in the human heart.

The heart was obtained from a patient, a violinist by occupation, forty-four years of age. He had a mitral stenosis and associated with the stenosis that common clinical condition, auricular fibrillation.

The electrocardiogram taken, through the courtesy of Dr. Horatio Williams, about a month before the patient died, showed not only that there was auricular fibrillation but also that the right ventricle of the heart was relatively more hypertrophied than the left. There have not been many instances in which it has been possible actually to confirm such an electrocardiographic record indicating hypertrophy of the right ventricle by a postmortem finding. This particular heart showed as great a relative right-sided hypertrophy as any which we have had an opportunity of examining. The sino-auricular node in this heart has (as you see), been cut out from the right auricle in the endeavor to locate, if possible, the lesion which caused the auricular fibrillation.

The left auricle presents an extensive calcification, so that the whole of it except the auricular appendix and the interauricular septum, feels like a bony plate; in fact, microscopic axamination shows that a portion of this plate is indeed undergoing an osteogenetic process. So far as I am aware, though new formation of bone has been found in many different organs in the body, yet, with the exception of the valves, it has only once been reported in the human heart. Poscharissky[1] found bone in the annulus fibrosis of the left ventricle.

Only three small blocks of tissue from the hard left auricular wall were sectioned and in one of these we encountered an area undergoing ossification. This area presents both calcified and non calcified osteoid tissue. The hard plate in the left auricular wall consists of hyaline degenerated connective tissue, much of which is calcified.

The lime deposit is distributed throughout the inner coat of the left auricular chamber, and the inner coat only, leaving the striated musculature untouched. For the most part it is in the shape of scattered granules and of plaques (diffusely impregnated tissue) bordered by coarse granules; but also, though more rarely, it is in the form of nodules possibly representing calcified atheromatous patches. The areas which stained blue with hæmatoxylin were tested for calcium, iron, fat and amyloid. By means of Roehl's method the deposit was proved to be calcific, and by means of the hydrochloric acid-potassium ferrocyanide test iron was also shown to be present, a finding which bears on the question of the relation between iron and calcification. (It should be stated that we did not use iron-free re-agents.) There was fat present throughout most of the section, but not particularly much in the calcified areas, so that no relation between the deposit of lime and a previous infiltration of fat was indicated. The test for amyloid proved negative. According to Poscharissky[2] an important point of resemblance between normal and pathological ossification is the presence of amyloid in the ground substance. The search by means of the orcein stain for elastic tissue in the calcific areas was not successful, probably because of the degenerated condition of the whole inner coat.

As was already stated, we found an ossifying area in the thickened, degenerated calcified endocardial coat of the left auricle. This area consists of a ground substance which stains well with eosin (osteoid ground substance) and of included nucleated elements. These included nucleated elements exhibit some shrinkage, and are surrounded by lacunæ with canaliculi indicated here and there; in brief, their transformation into true bone corpuscles is well under way. A vascular connective tissue lying in bays of the ossifying plaque seems to be invading it and causing its resorption. Erosion is indicated by the notches of the border of the plaque. Along the crenated border bounding the vascular connective tissue the matrix stains blue with hæmatoxylin-eosin, indicating calcification of the osteoid ground substance to form the matrix of true *bone*. The bays of young connective tissue included in the osseous plate, we consider marrow spaces, and the connective tissue itself primitive marrow. This marrow presents no osteoblasts or megalokaryocytes. It consists of a fine reticulum in the meshes of which are many blood vessels and some blood sinuses, numerous fibroblasts, some polymorphonuclear leucocytes and lymphoid cells, some cells with kidney-shaped nuclei and with eosinophilic granules, some cells which seem to be normoblasts, and not a few polynuclear giant-cells. These last lying in indentations of the ground substance, are evidenly osteoclasts. Indeed the osseous plaque seems to be undergoing lacunar resorption not only by means of the osteoclasts but also by means of the rest of the elements of the young vascular connective tissue such as the large blood sinuses, the blood vessels and free blood.

Apparently the osseous elements, inasmuch as they occur in the endocardial coat, were not being formed in connection with normal cartilage or bone-forming structures or from displaced embryonal cartilage or bone "Anlagen."* There are present in the inner coat of the left auricle the two features generally considered essential to bone-formation, namely, young connective tissue and lime. One may account for the presence of young connective tissue and lime as follows: We consider that a lesion, namely, a hyaline degeneration of practically the entire endocardial coat of the left auricle preceded the deposition here and there of lime salts. As to the young connective tissue it may possibly be inflammatory in origin, but it is more likely that the calcareous foreign body as such resulted in a reactive proliferation of vascular connective tissue, which in turn formed a young marrow in concavities of some of the lime plaques.

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*In explaining the presence of bone in such unexpected places as the circulatory system Bunting[3] says "one would turn naturally to the Cohnheim doctrine of embryonic displacement of tissue, were not the cases so numerous, and did not the figures just quoted show such a frequency of occurrence of the process in advanced arteriosclerosis."

Though we believe that the deposition of lime was conditioned by the local hyaline degeneration of the cardiac tissue, we must admit the possibility that an increased calcium content of the circulating body fluids *may* account for the lime deposit in the left auricle. We grant this possibility because we were unable to exclude it by an examination of the excretions during life or of the bones post-mortem. Moreover, in this case as in those of Davidsohn,[4] of Lazarus and Davidsohn[5] and of Verse,[6] the calcification is on the left side of the heart; and in these cases of calcium metastases it is deemed likely that the same chemical factors which so often result in calcification of the lung, have resulted in calcification on the left side of tthe heart in contradistinction to the right.

On the other hand in our case sections of the lung, kidneys, liver and spleen, free of lime as they are, indicate *that calcium metastasis played no role.*

The underlying cause for the hyaline degeneration of the endocardial connective tissue is unknown, nor is it clear in what way this lesion is associated with the auricular fibrilation.

The calcific ossifying plate is within the muscular layer, that is on the lumen side of the auricle, and the muscular layer must have been stretched over it. Under these conditions the muscle would probably be unable to contract down on this firm plate, and would consequently be paralyzed or be thrown into fibrillation. As soon as one auricle fibrillates, the musculature connections between the two are so intimate, that the other is at once thrown into a similar condition of incoördination. This is only an hypothesis of the mechanism by which auricular fibrillation may have arisen in this case.

A gross specimen of the heart and a slide showing an osteogenetic area in the calcific plate were presented.

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A PEDUNCULATED CARDIAC POLYP.

B. S. OPPENHEIMER, M.D. AND S. GEORGE EHRENREICH, M.D.

The following is an example of one of those rare, peculiar, solitary, organized thrombi in the heart, which are quite distinct from ordinary cardiac thrombi. It presented histological features which differed somewhat from those which have been described in other instances of similar formations.

The patient from whom the specimen was obtained was a pianist, fifty-three years old, who was admitted to Montefiore Home, March 18, 1912, in good general condition with slight symptoms of a chronic nephritis. On the 26th of March she had a sudden chill lasting over an hour, followed by a rise of temperature. This chill was repeated two days later, March 28. That afternoon she became very drowsy, and within the next few days she developed a complete opthalmoplegia of the left eye and a right-sided hemiplegia with Cheyne-Stokes respiration. A clinical diagnosis of cerebral embolism was made. Patient went into coma and died next day, March 31. Her death, as in cases of ball-thrombus, was not sudden but gradual.

The physical examination of her heart during life showed a slight enlargement to the left, accentuation of the second aortic sound, impurity of the first sound at the apex, but no murmurs,

The autopsy was performed by Dr. Ewing, to whom we are greatly indebted for the specimen.

The spleen and kidney presented multiple infarcts.

The brain showed a long decolorized clot in the left cerebral artery and partial softening of much of the brain tissue supplied by this vessel.

There was found attached to the posterior inferior border of the foramen ovale and projecting into the cavity of the left auricle, a pedunculated tumor which at that time was the size of a hen's egg (See fig. 1). It had been shrunken by alcohol and reduced in size by having a large section cut out of it. The surface was in parts smooth and shiny, in other parts covered with fibrin, and the cut section exhibited cencentric layers. Its pedicle was short and rather broad, measuring 1.5 cm. in diameter. The left auricle was hypertrophied and dilated; after preservation, its cavity measured 5.5 cm. in length, 4.5 cm. in width, and 4.5 cm. in depth. On the lateral endocardial surface of the left auricle there was a flat, firm, slightly elevated area about 2.5 cm. in length; otherwise the endocardium was smooth. There were no other thrombotic masses to account for embolism. The foramen ovale was not patent. The coronary arteries showed marked sclerosis with numerous calcareous plaques. At the time of the autopsy the pathological diagnosis of the growth rested between a thrombus, and a myxoma or sarcoma.

Microscopic section of the pedunculated tumor reveals a well organized thrombus with old and young connective tissue, blood vessels, pigment cells, some calcareous infiltration and interesting cords of endothelial cells which are interpreted as vascular sprouts.

The tumor springs from the septal wall of the left auricle in a region where the endocardium is thickened and vascularized. At the base of the short stalk there is a round celled infiltration. The pedicle itself consists of a very vascular connective tissue with pigment-bearing phagocytes.

The globular portion of the thrombus can be roughly divided into several areas. Nearest the stalk is a region characterized by long cords of endothelial cells which run transversely and roughly parallel with one another. These cords show a tendency to send off branches more or less at right angles, and in certain places in these branches the cells are arranged lengthwise along a lumen, apparently forming young capillaries. Between the endothelial cords are masses of pigment-cells. (See fig. 2.)

Distal to this region of cords of endothelial cells, the thrombus consists to a much greater extent of cells bearing pigment, which gives the staining reaction of hemosiderin. These phagocytes also give the staining for calcium with Roehl's method and fat with Scharlach R.

In this area and in the one further out there are rods stained deep blue with hæmatoxylin, which upon further study (with special stains) proved to be elastic tissue fibres that give positive reactions both for hemosiderin and calcium.

The region distal to the area of pigment-cells, consist of masses of polynuclear leucocytes and round cells.

Beyond this is an area consisting of a matrix with a very few cells, chiefly pigment cells. This matrix is the same as is found throughout the thrombus. It usually takes the eosin stain; sometimes the hæmatoxylin. In most parts it is fibrous in appearance, in other parts it is homogeneous, in still other parts it is flocculent. Staining reactions for mucin and for fibrin proved negative, as is not infrequently the case.

These four regions which consist prevailingly, the first of endothelial cords, the second of pigment-bearing cells, the third of pus cells, and the fourth of an almost non-cellular matrix, are not sharply defined strata. The different kinds of cells mentioned are found in the various parts of the thrombus, and in addition there are fibroblasts, plasma cells, resting-wandering cells and red blood cells. The polyp is not covered with endocardium.

There is as yet no hypothesis which satisfactorily accounts for these polyps but Bostroem's explanation of their origin in thrombosed varices of the interauricular septum seems to apply to at least a few of the cases.

Of the thirty-three cases collected from the entire literature since 1809 by Welch (of which at least twenty were typical instances,) four sprang from the left ventricle, four from the right auricle, and twenty-five from the left auricle, and usually from the septal wall, just as in the case here presented.

Discussion.

DR. EWING: At first I thought this process was a transformed myxoma, but have finally agreed with Dr. Oppenheimer that the condition is a simple pedunculated thrombus.

ILLUSTRATIONS.

FIG. 1.—Heart cut open, from the anterior aspect, showing the pedunculated thrombus in the left auricle.

FIG. 2.—Section from the pedunculated thrombus of the heart, showing a cord of endothelial cells which at one extremity arrange themselves lengthwise along a lumen; showing also the matrix of the thrombus with plasma and round cells and (at the bottom of the drawing) a group of pigment cells; (1) Endothelial cells arranged lengthwise along a lumen; (2) a cord of endothelial cells; (3) a group of pigment cells.

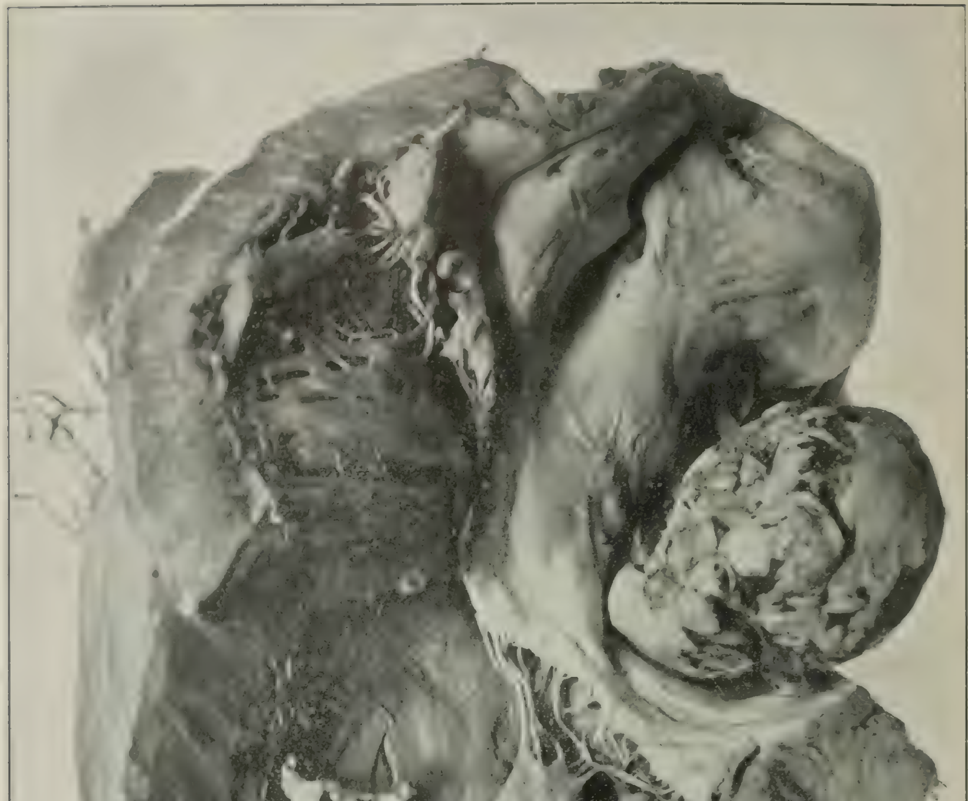

Fig. I.

Section from the pedunculated thrombus of the heart, showing a cord of endothelial cells which at one extremity arrange themselves lengthwise along a lumen; showing also the matrix of the thrombus with plasma and round cells and (at the bottom of the drawing) a group of pigment cells.

1 Endothelial cells arranged lengthwise along a lumen .....

2—A cord of endothelial cells ....

3—A group of pigment cells ....

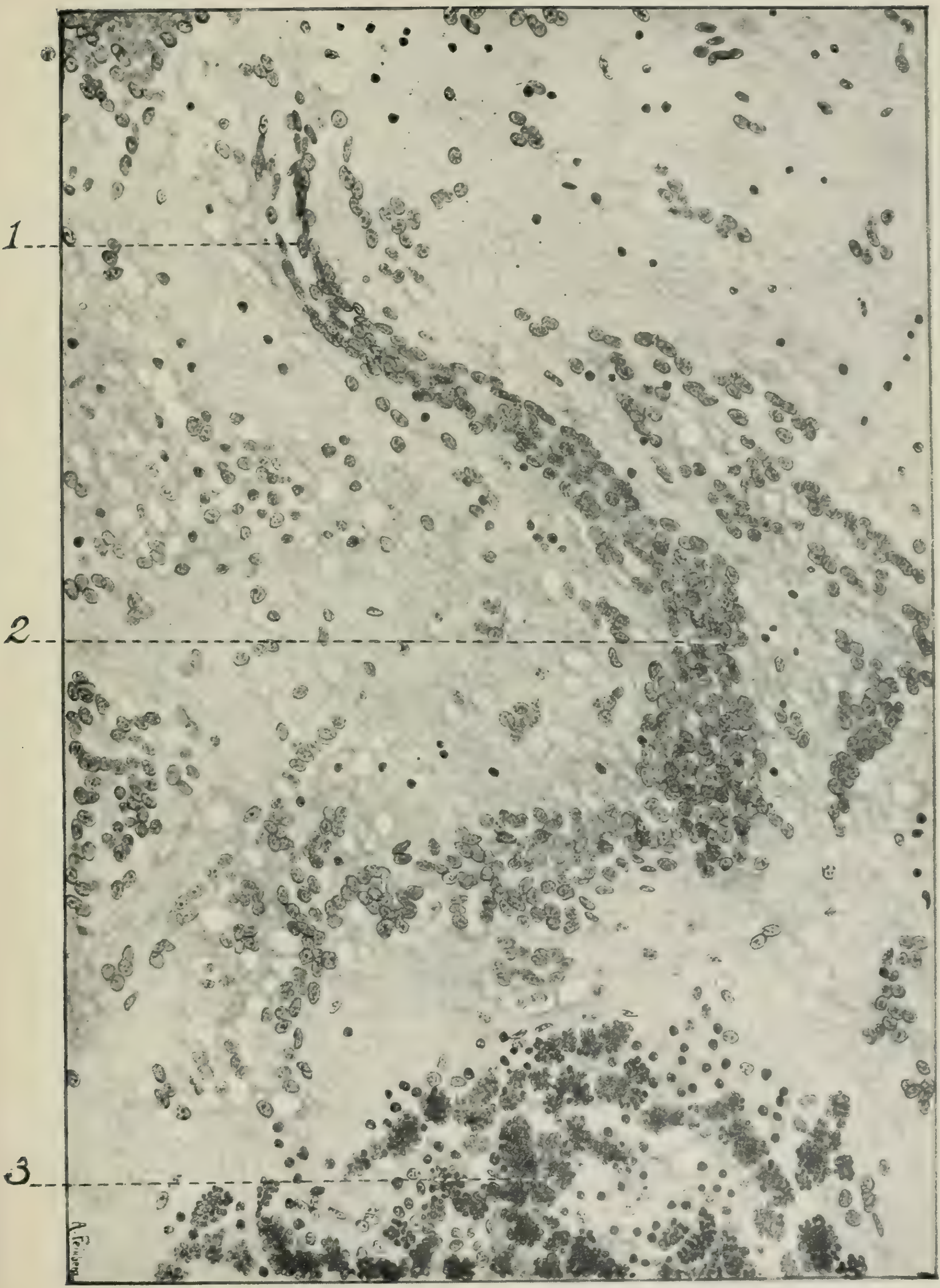

FIG. II.

ENDOTHELIOMA OF LYMPH-NODES.

JAMES EWING, M.D.

Dr. Ewing presented the clinical histories, stained sections, and photographs of a series of cases of endothelial hyperplasia and endothelioma of lymph-nodes, and drew the following conclusion from their study:

General Conclusions.

1. Extreme grades of endothelial hyperplasia are not infrequently associated with and dependent upon granulomatous infection of lymph-nodes, and these cases demonstrate the capacity of endothelium to respond to inflammatory irritation with extensive proliferation.

2. In some cases it is difficult or impossible to determine whether this overgrowth is simply inflammatory or independent of the irritant, autonomous and neoplastic.

3. The long-continued effect of granulomatous infection may lead to neoplastic growth of lymphatic endothelium; in the course of a granulomatous infection of lymph-nodes, after repeated operations, granulomatous elements may apparently be eliminated and the disease progress as a form of neoplasm.

4. Granulomatous infection of lymph-nodes may very early give rise to excessive overgrowth of endothelium of distinctly anaplastic type, and with local aggressive properties.

5. Such malignant endotheliomas may arise without any evidence of an associated granuloma. It is possible to conceive that an original infectious focus may be overgrown and obscured by the neoplastic cells. No definite evidence of such an event has been secured, but it has been shown that one node of a chain may exhibit purely neoplastic overgrowth, while others show chiefly granuloma.

6. Certain endotheliomas of lymph-nodes designated as diffuse plexiform, perivascular, or alveolar, are probably derived from the endothelium of lymph-sinuses and lymph-cords.

7. Certain primary tumors of lymph-nodes, with or without

associated granuloma, are probably derived from the reticulum cells of the follicles. These tumors resemble lymphosarcoma with large cells, and may be distinguished from tumors of small lymphocytes.

8. Endothelioma of lymph-nodes differs from other neoplasms in several particulars, and may be regarded as a disease *sui generis*, although nevertheless essentially neoplastic.

A SERIES OF CASES OF STAPHYLOCOCCUS AUREUS SEPSIS.

WILLARD B. SOPER, M.D.

The following report is based upon a series of cases collected from the records of St. Luke's Hospital, the Roosevelt Hospital and the Presbyterian Hospital. There were in all forty cases, in which the Staphylococcus Aureus was found in blood cultures, and which are unquestioned. There were twenty-nine deaths, with eight autopsies; and eleven recoveries.

Summary of lesions diagnosed clinically and at autopsy:

	Cases.	*Per Cent.*
Osteomyelitis	16	40
Pneumonia	12	30
Suppurative Arthritis	10	25
Cellulitis	10	25
Suppurative Nephritis	6	15
Carbuncle	6	15
Abscesses of Lungs	5	12.5
Suppurative Myocarditis	4	10
Suppurative Meningitis	3	7.5
Splenic Infarctions	3	7.5
Acute Vegetative Endocarditis	2	5
Thrombosis	2	5
Brain Abscess	1	2.5
Abscesses of Spleen	2	5
Perinephritic Abscesses	2	5

Course of Disease:

Of the twenty-nine cases with fatal outcome, twenty cases, or twenty nine per cent., showed a duration of fifteen days or less after onset. Of the remaining nine cases which died, only three survived one month. The recoveries, as was to be expected, showed a long duration; the shortest six weeks, the longest six months, with the majority about three months.

Conclusion as to Treatment:

There seems to be a fulminant type or rather one in which either the infection is overwhelming or the resistance markedly low. This type is of a frequency about equal to that of the less severe type—in this series the figures standing about twenty to twenty. With this type, which is represented clinically by an excessive toxæmia and a larger number of colonies where blood plates are made, the prognosis is extremely grave. However, the number of recoveries in this series, coupled with the often remarkably rapid disappearance of cocci from the blood following removal of the infective focus, demonstrates that no case is hopeless provided the infective focus can be reached by the surgeon.

Discussion.

DR. E. LIBMAN: In a discussion of Dr. Soper's paper which I gave before the Medical Section of the Academy of Medicine some time ago, I made an error in stating that I had seen 150 cases of staphylococcus aureus general infection. In looking over my records I find that I have 130 odd cases. A number of years ago I read a paper before this society on a study of twenty-three cases.

In children the staphylococcus aureus circulating in the blood has a special predilection to lodge in the bones and that explains the frequency of acute osteomyelitis in children as compared to the same disease in adults.

Dr. Soper has reported a case of general infection in diabetes. Such cases in my experience are not very common. It is a curious fact that whenever one has a focus in the body containing carbohydrates it is uncommon to find a general infection One almost never gets a general infection due to a pylephlebitis, but it is much more frequent in infections of the duct system of the liver.

In staphylococcus infections of the lactating breast I have not seen a single case of general infection in ten years, no matter how severe the clinical picture was.

In staphylococcus infections of the endocardium the cardiac phenomena play very little role, because, as a rule, the cases terminate so rapidly. Often one finds only a small deposit of fibrin on one of the valves or on the endocardium of the ventricle.

General infections in the puerperal period, due to the staphylococcus aureus, are very uncommon. When they do occur the entering point seems to be more in the cervix or vagina, rather than in the uterus.

I have never seen a case of lobar pneumonia due to the staphylococcus. The lesions found in the lungs in cases of general infection by the staphylococcus are rather characteristic and look like hemorrhagic furuncles, the central purulent point often being quite small. There is no great tendency for the staphylococcus to multiply in the blood stream. The chance of recovery depends to a great extent on whether the local foci which are causing the general infection can be dealt with surgically in a satisfactory manner or not.

When the staphylococcus albus is found in the blood in large numbers and no primary inflammatory focus can be found, the prognosis is usually exceedingly bad. In such cases the staphylococci have evidently entered from the intestine or other mucous membranes or from the skin and multiply in the blood because the patient has no resistance.

Dr. MacCallum: I was once very much impressed by a case of staphylococcus albus infection in which the focus of infection was from a very slight scratch of the skin.

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